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Takotsubo syndrome: an overview of pathophysiology, diagnosis and treatment with emphasis on cancer patients

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Abstract
Takotsubo syndrome is a disease of great clinical importance that remains underdiagnosed. It is a form of acute heart failure characterized by a transient wall motion abnormality of the left ventricular apex typically triggered by emotional or physical stress. Takotsubo syndrome is commonly associated with cancer and results in poor outcomes. Therefore, early recognition and prompt therapy are essential to improve prognosis. The aim of this manuscript is to review the consequences of the association between cancer and Takotsubo to summarize the available evidence to guide physicians to improve the management of these patients.

Keywords Takotsubo syndrome · Cancer · Heart failure

Introduction

Takotsubo syndrome (TS) was originally described in 1990 by Sato et al. and is characterized by acute and reversible (< 21 days) left ventricular (LV) dysfunction with a clinical pattern similar to acute coronary syndrome, i.e., generally abrupt onset of precordial pain and dyspnoea without the evidence of an obstructive coronary disease [1–3]. The presence of LV regional wall motion abnormalities characteristically extending beyond a single epicardial coronary artery distribution defines the syndrome [4].

Several stressors have been identified as triggering the syndrome and may occur in a variety of settings and clinical contexts, such as accidents, unexpected deaths, quarrels and life-changing diseases and events, or physical stressors, such as neurological events, septic shock and gastric ulcer with copious bleeding. In addition, malignancies and tumours, such as pheochromocytoma or paraganglioma, are also described as triggers of TS [5, 6].

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Cancer might affect the occurrence and prognosis of TS. Previous studies have shown higher mortality and morbidity rates and increased length of hospital stay and costs [7, 8]. The aim of this review is to perform a comprehensive analysis of TS in cancer patients, focusing on diagnostic approach and therapy.

TS and cancer

In recent years, there has been a great interest in studying the relationship between cancer and TS mainly after a few published studies demonstrated a strong association between these two conditions [9–13]. We performed an extensive search in the PUBMED database to identify studies that showed associations between cancer and TS from 1974 to February 2019. The search was performed using the words "Takotsubo" and "Cancer" or "Malignancies"; "Takotsubo Syndrome" and "Cancer" or "Malignancies"; Takotsubo Cardiomyopathy" and "Cancer" or "Malignancies"; "Stress-Induced Cardiomyopathy" and "Cancer" or "Malignancies".

We identified 433 articles (Fig. 1). We excluded 217 studies given the lack of an association between these two diseases or the inclusion of experimental studies; 37 articles were letters or editorials and 3 articles were not published in English. We reviewed 176 studies, but we excluded 145 case reports and 16 studies because they did not adequately report patient information. Finally, in this review, we included 15 articles and summarized the clinical characteristics and results in Tables 1 and 2.

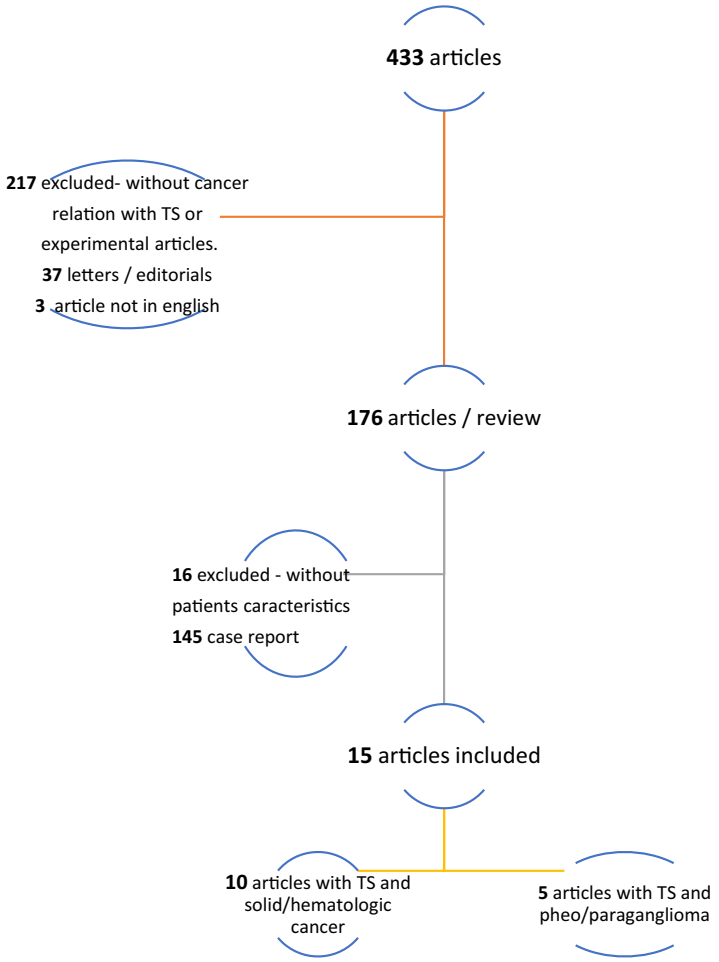

Fig. 1 Flowchart of Literature search. TS = Takotsubo syndrome; pheo = pheochromocytoma

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Epidemiology

The prevalence of neoplasms seems to be higher in patients with TS compared with individuals of the same age group and sex both at the time of disease diagnosis and during follow-up [13]. Burgdorf et al. showed that among 50 patients with diagnosis of stress cardiomyopathy, 18% had cancer at the time of diagnosis, and a malignancy was discovered in 14% during the follow-up of 2.8 years [10]. Satter et al. similarly showed that during the follow up of 1529 ± 1121 days, 11 (9.6%) patients were newly diagnosed with malignant disease [11].

In a large study of TS, the prevalence of malignancy was 1.3% in TS patients [14]. Joy et al. in a study with 122,855 patients with TS showed that 6.6% of the patients had cancer [16]. Others recent observational studies have showed a higher prevalence of malignancy in TS patients. Satter et al., Giza et al. and Zaghlol et al. showed a prevalence of 14%, 23.3% and 25.5%, respectively [11, 12, 22]. This increase in prevalence may be due to a greater knowledge of the association between the diseases and an increase in the diagnosis. As a result, the incidence of TS in cancer patients has increased in recent years [12, 16].

Similar to the general population, a higher prevalence of TS is described in women [11, 12, 22]. The prevalence is highest in postmenopausal women, patients aged 67 to 73 years old and patients with risk factors for cardiovascular disease [7, 11, 13, 23]. Brunetti et al. observed that the most prevalent tumours were gastrointestinal cancer (including oesophagus, glands and biliary ducts) in 23% of the patients, followed by breast and lung (both 17%) and by hematologic and skin tumours (10% for each). Two other studies cite colorectal cancer as one of the most associated with TS (prevalence 14% - 29%) [24, 25]. Haematological neoplasms were less prevalent and had similar prognostics compared with solid neoplasms [13].

Pathophysiology

The pathophysiology of Takotsubo syndrome is complex and involves several mechanisms not yet fully elucidated. The most accepted hypothesis reflects the integrated and systemic physiological responses to acute and severe stress and cardiovascular responses to sudden elevations in endogenous or exogenously

Table 1 Resume of clinical features of patients with Takotsubo syndrome and cancer included in articles reviewed

Authors	Type studies	No. of patients with TS and cancer	Age	Sex	Type of tumour	LVEF	Triggers	Results
Brunetti ND et al. [8]	Meta-analysis	8258	Mean range 67–72 years	F 7268 (88%)	Solid and hematologic	–	Physical stressor 4789 (58%)	Either history of or current cancer are associated with an in- creased risk of adverse events in TTS patients.
Zaghlol R et al. [14]	Retrospective	81	Mean ± SD 70.0 years ± (10.6)	F 69 (80%)	Solid and hematologic	LVEF < 40% in 72 (89%)	Unknown	Cancer is associated with lower LVEF on presentation, longer hospitalization and higher rate of in-hospital cardiac arrests.
Desai R et al. [7]	Retrospective	562	Mean ± SD 62.6 years ± 12.1	F 388 (69.1%)	Solid and hematologic	–	Chemotherapy 100%	TS incidence among adult patients receiving chemotherapy, which adds to significantly increased in-hospital mortality and healthcare finances
Möller et al. [15]	Prospective	56	Mean ± SD 73.0 years ± 8.1	F 48 (85,7%)	Solid	Mean ± SD 42.1 ± 10%	Emotional 14 (25%) Physical 28 (50%)	The prevalence of malignancy in patients with TS is high and considerably exceeds that in the normal population. Cancer is major determinant of long-term mortality in TTS.
Joy PS et al. [16]	Retrospective	8089	18–34 years: 0,7% 35–49 years: 4,3% 50–64 years: 29% 65–79 years: 48.4% > 80 years: 17.6%	F 6584 (81.4%)	Solid and hematologic	–	Unknown	All-cause mortality was significantly higher in TS patients with cancer.
Sattler K et al. [17]	Prospective	17	Mean ± SD 69 years ± 11	F 13 (76.5%)	Solid and hematologic	Mean ± SD 36 ± 10%	Unknown	Patients with TS and cancer lower LVEF than patients with MI and cancer. Incidence of atrial fibrillation was higher in TS patients. In patients suffering from cancer, mortality was higher in TS patients than in MI patients as well, and was predominantly caused by non-cardiovascular events.
Giza, DE et al. [12]	Retrospective	30	Mean ± SD65 years ± 9	F 22 (73,3%)	Solid and hematologic	Mean ± SD 35 ± 8%	Surgical 8 (32%) Acute illness 3 (12%) Chemotherapy 5 (20%) Emotional stress 7(28%) Radiation 1 (4%)	Patients with advanced cancer developed more complications after TS because of their frailty and reduced reserves. In the follow-up the survival rate was reduced because of the poor cancer prognosis.
Sattler, K et al. [11]	Retrospective	25	Mean ± SD 66.7 years ± 11.4	F 17 (68.0%)	Solid and hematologic	Mean ± SD 34.9 ± 9.9%	Emotional stress 5 (20%) Physical stress 15 (60%)	Cancer was associated with a negative outcome during a mean follow up time of 4.2 years. A low LVEF was predictive for increased occurrence of cardiogenic shock.
Girardey M et al. [13]	Retrospective	44	Mean ± SD 68 years ± 10	F 29 (65.9%)	Solid and hematologic	Mean ± SD 36 ± 12%	Emotional stress 5 (11.4) Physical stress 31 (70.5)	The main findings were that among patients presenting with TS, those with cancer showed higher peak BNP and higher mortality rate. The diagnosis of malignancy in patients with TS was an independent predictor of cardiac and all-cause deaths.

Table 1 (continued)

Authors	Type studies	No. of patients with TS and cancer	Age	Sex	Type of tumour	LVEF	Triggers	Results
Burgdorf, C et al. [10]	Retrospective	14	Median 70.9 years (58–84)	F 12 (85%)	Solid and hematologic	Patients with chemo 46 ± 8%. Patients without chemo 42 ± 5%.	Unknown	TS is associated with diverse malignancies in the sense of a yet not noticed paraneoplastic disease. The long-term prognosis of patients with TS is no better than patients with acute MI and thus, TS should no longer be regarded as a benign disease.

administered catecholamines [2, 3]. This release of catecholamines appears to play a central role in triggering TS.

The pathophysiology of this syndrome is typically explained in two stages. The first stage starts with the increased release of epinephrine and norepinephrine generated by the cognitive centres of the brain through the activation of the hypothalamic-pituitary-adrenal axis (HPA) in response to a certain stress via a process named HPA gain. Serum catecholamine concentrations are substantially elevated in TS presentation compared with baseline levels in the same patients, and these levels are comparable to those noted in patients with acute heart failure secondary to acute myocardial infarction [5]. These differences suggest the potential for excessive HPA gain and release of epinephrine in susceptible individuals [2].

The second step is the cardiovascular response to increased circulating catecholamines. At this stage, three main hypotheses are implicated in the development of TS: multiple-vessel vasospasm, direct catecholamine-mediated myocardial stunning and increased ventricular afterload. These hypotheses do not appear to occur simultaneously in some patients and are not mutually exclusive [26].

Some patients with TS have high levels of endothelin. This peptide is an extremely potent vasoconstrictor and may be a potential mechanism for triggering vasospasm of multiple vessels [27]. In addition, after any stress and catecholamine release, the generalized impairment of endothelial function secondary to oxidative stress is expected. Coronary and peripheral arteries may therefore be subject to vasospasm after increased stimulation by catecholamines.

Myocardial stunning mediated by catecholamines can be explained by the β2-adrenoceptor hypothesis. This hypothesis is based on the observation of apical-basal gradients of sympathetic nerve endings and β-adrenoceptors in mammalian hearts. In several mammalian species, including humans, higher densities of the sympathetic nerve are noted in the basal myocardium compared with the apex [17]. The location of cardiac sympathetic nerve terminals therefore does not explain apical hypokinesia, the most common anatomical variant of TS; however, this characteristic may play a role in the basal variant [2].

The circulatory and systemic peripheral responses to acute catecholamine administration are accentuated with hypertensive peaks, which cause the myocardium to remain in a hypercontractile state for a few minutes. The physiological state evolves to a secondary stage when acute apical dysfunction develops on a background of normotension or hypotension and is often complicated by cardiogenic shock and persistent vasoconstriction or paradoxical vasodilation [28]. Increased wall stress transmitted by high intracavitary pressure may result in regional dysfunction.

In addition, in TS, the endomyocardial capillary density is substantially reduced mainly due to the expansion of the extracellular matrix. Ultimately, these changes result in a mismatch between supply and demand of oxygen in cardiac

Table 2 Resume of clinical features of patients with Takotsubo syndrome and pheochromocytoma/paraganglioma tumours included in articles reviewed

Authors	Type studies	No. of patients with T and cancer	Age	Sex	Type of tumour	LVEF	Triggers	Results
Gagnon, N et al. 2017 [18]	Retrospective and systematic review	63	F 51 years (28–81) M 46 years (25–86)	F 42 (67%)	Paraganglioma Pheochromocytoma	LVEF ≤ 30% in 20 (56%) cases	Surgery 8 (12%) Emotional stress 4 (6%) Other 7 (11%)	Complications were described in 32 patients (51%) and included cardiogenic shock (8.3%), acute renal failure (5.2%), arrhythmia (10.3%) and death (5.2%). Recurrence of TS did occur in 9 (14%) cases.
Zaghlol R et al. 2019 [14]	Systematic review	30	Mean ± SD 51.8 ± 17.5 years	F 23 (61%)	Pheochromocytoma	Mean ± SD 29 ± 7%	Physical stress 30 (100%)	Pheo-induced different types of cardiomyopathy. Early resection may prevent progression to irreversible myocardial remodelling and death.
Hassan SY. 2016 [19]	Retrospective and systematic review	80	Mean ± SD 46.53 years ± 15.6	F 56 (70%)	Pheochromocytoma	Mean ± SD 27.7 ± 11.6%	Emotional stress 0 (0%) Physical stress 80 (100%)	Recurrence of TS in the Pheo-TS cohort of patients occurred in 14 of 79 cases (17.7%) with available information.
Batisse-Lignier, M. et al. 2015 [20]	Systematic review and meta--analysis	49	Mean ± SD 44.6 years ± 16.1	F	Pheochromocytoma Paraganglioma	Mediaan 30.0 (23.0–35.0)	Emotional stress 0 (0%) Physical stress 49 (100%)	Pheo and paraganglioma can lead to chronic and acute cardiomyopathies with the same acute and life-threatening clinical onset.
Agarwal V et al. 2011 [21]	Systematic review	38	Mean ± SD 50.3 years (± 16.4)	F 27 (71.1%)	Pheochromocytoma	Mean ± SD 28.7 ± 5.8%	Emotional stress 4 (10.5%) Physical stress 7 (18.4%)	The similarities in the clinical course and outcomes of patients with TS and Pheo with respect to patients with TS without

myocytes. Ultrastructural analysis of myocardial tissue clearly showed intracellular vacuoles and the accumulation of ubiquitin in the myocardial samples obtained during the acute phase of TS. These results indicate a potential oxygen deficiency that contributes to cardiomyocyte dysfunction [26].

Another important aspect of TS is the fact that it occurs more frequently in postmenopausal women. This finding is probably explained by the reduction in oestrogen levels. This hormone reduces the inotropic and chronotropic response to catecholamines, alters vascular reactivity and is cardioprotective [5, 26].

As mentioned above, the main mechanism of the physiopathology of TS involves the action of catecholamines in the myocardium. Cancer increases neurohormonal activation and perpetuates a chronic inflammatory state with release of cytokines, reactive oxygen species, prostaglandins and catecholamines, which could theoretically contribute to the pathogenesis of the development of stress cardiomyopathy [10]. Patients with malignancy have a reduced tolerance threshold for stressors and an increased sensitivity of cardiac adrenergic receptors. In this scenario, the addition of physical stressors (for example, pain secondary to cancer, diagnostic procedures and oncological surgeries) and emotional stressors (for example, fear of illness or death and changes in the familiar dynamic) common to the disease contributes to a greater predisposition to develop TS in these patients.

Diagnosis

Clinical presentation

Patients with Takotsubo syndrome usually present to an emergency department with acute chest pain of cardiac origin (angina), breathlessness and palpitations. Sinus tachycardia or arrhythmia may be present. In more severe cases, presyncope or syncope due to ventricular tachyarrhythmias, severe left ventricular outflow tract obstruction (LVOTO), or cardiogenic shock may occur [5, 29].

Some studies classified TS as primary or secondary. Primary TS includes patients who develop the syndrome, and the reason is not clear but could involve an emotional stress. In secondary TS, there is a sudden activation of the sympathetic nervous system, leading to an increase in circulating catecholamines. Secondary TS typically occurs in patients hospitalized for another reason, such as sepsis, surgical, obstetrical, or anaesthetic procedures [3].

The initial clinical presentation of cancer patients is similar to the general population with chest pain and/or dyspnoea representing the most common symptoms [12, 13]. Baseline characteristics, such as race, medical or social history, did not differ from patients without cancer [16, 22]. Joy et al. showed that the cardiovascular factors (hypertension, diabetes and morbid obesity) and coronary arterial disease were less prevalent in cancer patients, but the Charlson's Comorbidity Index indicated more severity probably due to the risk associated with cancer [16].

TS may be misdiagnosed as acute coronary syndrome (ACS) given the similarities in clinical presentation. TS should therefore be considered as a differential diagnosis in patients presenting with clinical features of ACS. Some clinical differences observed between TS and ACS may aid in obtaining the correct diagnosis. Patients with TS present higher heart rate and more ECG abnormalities (ST elevation, QTc prolongation) than patients with myocardial infarction (MI). The left ventricle ejection fraction was lower in TS compared with MI. Regarding previous medical history, patients with MI had more "traditional" pro-atherogenic risk factors, such as diabetes, hypertension or obesity, than patients with TS [24].

Triggers

The typical description of TS includes the presence of a preceding mental or physical stress. The syndrome is preceded by a trigger factor in approximately 70% of patients [14]. Mental stress includes unexpected deaths, receiving news of serious diagnosis or work-related problems. Physical stress includes asthma attack, non-cardiac surgery and in particular neurological events, such as subarachnoid haemorrhage, stroke and seizure. Other related conditions include acute respiratory failure, malignancy and septic shock [15].

In this article, we describe the most common triggers in cancer patients (Fig. 2). The review articles showed that the physical stressors are more prevalent than emotional stressors in cancer patients, and the most common stressors include surgical stress, chemotherapy and radiotherapy [8, 11, 12, 25]. Physical stressors are also more often reported in cancer patients (58%) compared with controls (44%) [($p = 0.0058$)] [8].

A few studies analysed the incidence of TS after exposition to different chemotherapy [12, 23, 30, 31]. The mean overall incidence of TS in patients receiving chemotherapy was 53 per 100,000 chemotherapy-related hospitalizations [7]. Several chemotherapeutics regimens have been described in TS precipitants, such as 5-fluoracil (5-FU), capecitabine, trastuzumab, bevacizumab, rituximab and more recently immunotherapy [23, 31–33]. Cardiotoxicity is a known adverse effect of 5-FU and occurs in 1.2% to 18% of patients who receive the agent, but the mechanism of cardiotoxicity from 5-FU is not well established. Many reports of cardiotoxicity describe coronary ischaemia that is thought to result from vasospasm. However, in recent years, there have been an increasing number of accounts of 5-FU associated with TS, and the differential from ACS is important in these patients [32, 34].

Immune checkpoint inhibitors (ICIs) have improved the management and the prognosis of several cancer types. The administration of ICIs could lead to immune-related adverse

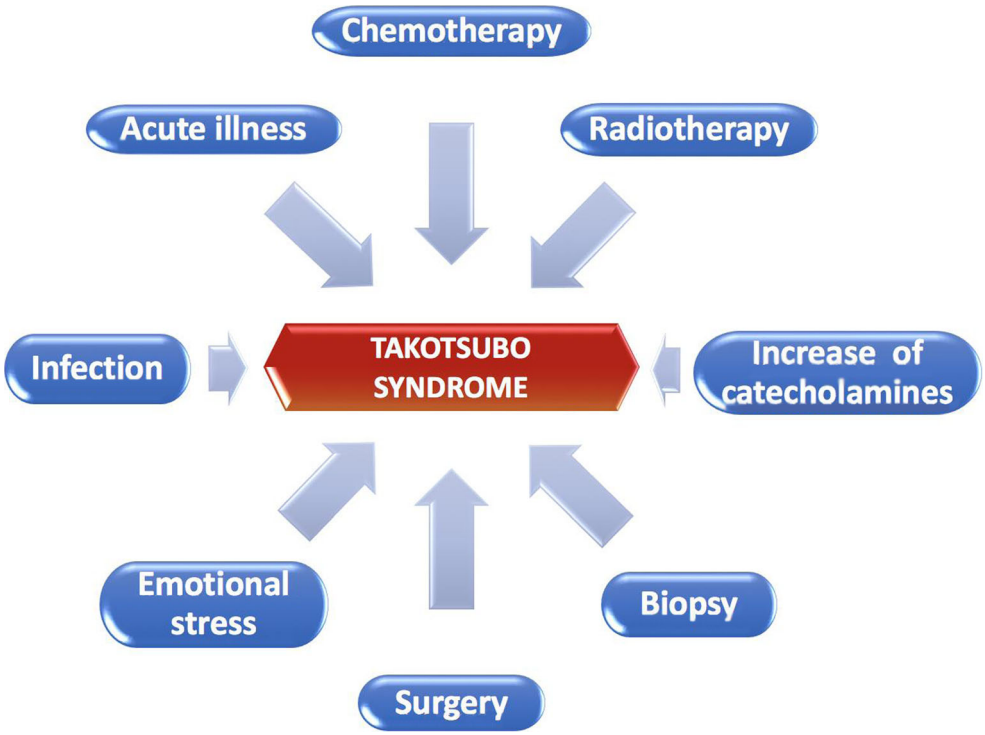

Fig. 2 The most common triggers in Takotsubo Syndrome

events in many organs. Cardiotoxicity is rare but potentially fatal. The main manifestation is myocarditis, but the number of TS reports in these patients is increasing. The differential diagnosis of myocarditis and TS is occasionally difficult to perform and CMR an important diagnostic tool in this scenario [33, 35].

Desai et al. showed that patients receiving chemotherapy or immunotherapy for neoplastic conditions who develop TS had two times higher odds (odds ratio [OR] 2.17, 95% confidence interval [CI] 1.68 to 2.80, $p < 0.001$) for in-hospital mortality [7]. In addition, this study showed that patients on chemotherapy who develop TS had longer hospital duration of hospital stay and higher hospital costs [7].

Cancer patients are often submitted to surgical procedures for tumour diagnosis or treatment. Many factors during the procedures may increase catecholamines and result in an increased occurrence of TS during the perioperative period, such as anxiety for the surgery, operative blood loss, long operative time, subjective surgical difficulty, postoperative pain and complications. Thus, surgery is a frequent trigger of TS [12, 36].

Mediastinal radiation therapy is frequently used in patients with lymphomas, cancer of the oesophagus and breast cancer and is related to the development of cardiotoxicity affecting coronary artery disease and pericardial diseases. Some case reports have reported radiotherapy as a TS trigger [12, 37].

Other potential triggers of TS include pain, metabolic disturbances and dehydration. Chronic and acute cancer-related pain may increase the susceptibility to sympathetic activation, whereas vomiting, fever, anaemia or bleeding, which are very common in cancer patients, may induce volume depletion, leading to cardiac hyperkinesia and afterload increase and subsequently predisposing to TS [38, 39].

Many studies in the literature could not clearly identify the triggering factor of TS. One possible explanation is that most cancer patients are simultaneously exposed to these factors previously mentioned and chronically suffer from great physical and emotional stressors. Thus, multiple combined factors are likely involved. In addition, the emotional stressor might be underdiagnosed [6].

Exams

The diagnosis of TS can be made through the use of diagnostic criteria incorporating anatomical features, ECG changes, cardiac biomarkers and reversibility of myocardial dysfunction (Table 3) [3]. The most used criteria for the diagnosis are the Mayo Clinic Criteria. More recently, the International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria) were incorporated in clinical practice [4, 6]. Patients should be submitted to a resting 12-lead electrocardiogram. Electrocardiographic (ECG) abnormalities are described in 95% of cases during the acute phase of TS and usually consist of ST segment elevation or depression, Q waves with deep and T wave inversion and significant QT prolongation [40].

The initial approach must include the measure of cardiac biomarkers. Cardiac troponins T or I are typically elevated, but the peak is not very high. Characteristically, we observed a

Table 3 Diagnostic criteria for stress cardiomyopathy according to Heart Failure Association of the European Society of Cardiology, InterTAK Diagnostic Criteria and Mayo Clinic Criteria

Heart Failure Association - European Society of Cardiology Criteria

- Transient regional wall motion abnormalities of LV or RV myocardium, which is generally preceded by a stressful trigger (emotional or physical).
- The regional wall motion abnormalities usually[a] extend beyond a single epicardial vascular distribution and often result in circumferential dysfunction of the ventricular segments involved.
- The absence of culprit atherosclerotic coronary disease (including acute plaque rupture, thrombus formation and coronary dissection) or other pathological conditions to explain the pattern of temporary LV dysfunction observed.
- New and reversible electrocardiography abnormalities (ST segment elevation or depression, LBBB,[b] T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).
- Significantly elevated BNP or NT-proBNP during the acute phase.
- Positive but relatively small elevation in cardiac troponin (i.e., disparity between the troponin level and the amount of dysfunctional myocardium present).[c]
- Recovery of ventricular systolic function on cardiac imaging at follow-up (3 to 6 months). +

International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)

- Patients show transient[d] LV dysfunction (hypokinesia, akinesia or dyskinesia) presenting as apical ballooning or midventricular, basal or focal wall motion abnormalities. RV involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal Takotsubo syndrome).[e]
- An emotional, physical, or combined trigger can precede the event, but it is not obligatory.
- Neurological disorders (e.g., subarachnoid haemorrhage, stroke, seizures) as well as pheochromocytoma may serve as a trigger.
- New ECG abnormalities are present (ST segment elevation or depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.
- Levels of cardiac biomarkers are moderately elevated in most cases; significant elevation of BNP or NT-proBNP is common.
- Significant coronary artery disease is not a contradiction in Takotsubo syndrome.
- Patients have no evidence of infectious myocarditis.[e]
- Postmenopausal women are predominantly affected.

Revised Mayo Clinic Criteria

- Transient hypokinesis, akinesias or dyskinesis of the LV mid-segments with or without apical involvement; the regional wall abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.[f]
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.[g]
- New ECG abnormalities (either ST segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
- Absence of pheochromocytoma or myocarditis.

Adapted table from: Medina de Chazal H, et al. J Am Coll Cardiol. 2018;72 [22]:1955–71

LV left ventricle, *RV* right ventricle, *LBBB* left bundle branch block, *BNP* B-type natriuretic peptide, *NT-proBNP* N-terminal pro-B′type natriuretic peptide

[a] Acute, reversible dysfunction of a single territory has been reported

[b] Left bundle branch block may be permanent after Takotsubo syndrome, but should also alert clinicians to exclude other cardiomyopathies. T-wave changes and QTc prolongation may take months to normalize

[c] Troponin-negative cases have been reported, but are atypical. + Small apical infarcts have been reported. Bystander subendocardial infarcts have been reported, involving a small proportion of the acutely dysfunctional myocardium. These infarcts are insufficient to explain the acute regional wall motion abnormality observed

[d] Wall motion abnormalities may remain for a prolonged period of time or documentation of recovry may not be possible

[e] Cardiac magnetic resonance imaging is recommended to exclude infectious myocarditis and diagnosis confirmation of Takotsubo syndrome

[f] There are rare exceptions to these criteria, such as those patients in whom the regional wall abnormality is limited to a single coronary territory

[g] It is possible that a patient with obstructive coronary disease may also develop Takotsubo syndrome. However, this is very rare, perhaps because such cases are misdiagnosed as an acute coronary syndrome. In both of the above circumstances, the diagnosis of stress cardiomyopathy should be made with caution, and a clear stressful trigger must be sought

discrepancy in troponin levels with a degree of ventricular dysfunction in these patients [4]. Troponins have an additional prognostic value, suggesting that higher levels were predictors of worse prognosis. Creatine-kinase myocardial band (CK-MB) increases are typically discrete and present with smaller values than those observed in the ACS [41].

Serum cardiac natriuretic peptides (BNP and pro-BNP) are a marker classically used for the diagnosis of decompensated

heart failure. In TS patients, high BNP levels are concordant with the degree of ventricular dysfunction, and this feature is different from what occurs in patients with ACS [42]. Given these differences, the combination of troponin, CK-MB and BNP is recommended to discriminate TS and ACS [4].

Many inflammatory markers are being studied to help to characterize the syndrome. C-reactive protein levels are elevated in general, suggesting that inflammatory state is present in this scenario. Interleukin-6, interleukin–7 and a signature of circulating microRNAs (miR-1, miR-16, miR-26a, and miR-133a) are being tested in TS to differentiate early TS from ACS patients [41, 43].

Some particularities are noted in cancer patients with TS syndrome. Serum natriuretic peptide (BNP) levels are higher in cancer patients compared with those without cancer [11, 12]. Patients with malignancy had lower levels of haemoglobin and higher levels of C-reactive protein [11]. These findings are consistent with the increased severity of the syndrome observed in cancer patients.

Echocardiography is the method of choice for evaluation of left ventricular function and visualization of symmetric regional wall motion abnormalities, especially in unstable patients and in the acute phase of the syndrome [41]. Patients with TS have lower initial left ventricle ejection fraction (LVEF) than patients with ACS [24, 37].

Classically, TS has been described as apical ballooning cardiomyopathy characterized by hypo-, a-, or dyskinesia of mid-apical myocardial segments and occasionally associated with hypokinetic mid-segments. The anterior or entire interventricular septum and inferior or midventricular anterolateral wall may also be involved [4, 44]. The formation of apical ballooning continues to be the most prevalent type of the syndrome (prevalence of 75 to 80%), including cancer patient [4, 25].

The apical ballooning type is associated with typical complications of TS. Due to apical akinesia, this type is predisposed to develop apical thrombus. In addition, basal hyperkinesia may cause dynamic left ventricular outflow tract obstruction (LVOTO) mainly in patients with pre-existing septal bulge, which further reduces stroke volume and is associated with mitral regurgitation (MR) due to systolic anterior motion of the mitral leaflet. MR is estimated to be present in 14–25% of TS patients [45, 46].

Others morphologic variants usually described as TS include midventricular, basal or inverted, focal dysfunction and biventricular TS (Table 4). Midventricular TS is the second more prevalent form and is described by hypo-, a- or dyskinesia of midventricular segments, often resembling a cuff [47]. Midventricular TS is present in 10% to 20% of patients and is associated with a more severe reduction in cardiac output and cardiogenic shock [4].

The basal or inverted forms are characterized by exclusive involvement of basal segments. This variant is present in less than 5% of patients and appears commonly in pheochromocytoma patients [21]. The focal TS variant is difficult to differentiate from ACS and myocarditis because it usually presents a smaller reduction in LVEF, focal segmental deficit (anterolateral segments is the most common) and great potential recovery [47]. The biventricular variant is rare, and the diagnosis is occasionally difficult given the atypical nature of the compromised right ventricle. This form is usually associated with severe haemodynamic impairment and poor prognosis [4].

Measurement of LVEF by echocardiography should be repeated after approximately 3–4 weeks to assess the degree of recovery. The majority of the population studied had incomplete recovery of the LVEF after the event (initial LVEF of 62.6% and 56.8% after recovery, $p = 0.0141$) [12]. Patients

Table 4 Anatomical variants of Takotsubo syndrome

Variant	Prevalence	Anatomical description	Complications
Apical ballooning (typical)	75–80%	Hypo-, a- or dyskinesia of mid-apical myocardial segments is typical, sometimes associated with hypokinetic mid--segments. The anterior or entire interventricular septum, inferior or midventricular anterolateral wall may also be involved.	Left ventricular outflow tract obstruction and/or apical thrombus formation
Midventricular	10–20%	Hypo-, a- or dyskinesia of midventricular segments, most often resembling a cuff.	Severe left ventricular dysfunction
Basal or inverted	5%	Only basal segments are involved	Less severe hemodynamic compromise
Biventricular	< 0.5%	Right ventricular involvement is characterized by RV dilatation with hypo- to akinesia of the free wall and apex in its isolated form.	Severe haemodynamic compromise and cardiogenic shock
Focal dysfunction	Rare	Mostly involving an anterolateral segment has been described	Benign course, more commonly associated with chest pain

Adapted table from: Medina de Chazal H, et al. J Am Coll Cardiol. 2018;72 [22]:1955–71

with severe ventricular dysfunction are less likely to recover the ejection fraction. Only 22% of patients with initial LVEF < 25% exhibited recovery of the LVEF at follow-up [22].

Two-dimensional echocardiography speckle-tracking (2D-ST) imaging should be performed in TS patient evaluation. The global longitudinal strain and radial is lower in these patients at baseline and improved in patients upon follow-up [48]. There was a significant apex-to-base gradient of strain at baseline, indicating more severe involvement of the apical and to a lesser extent midventricular segments compared with the LV base [48, 49].

Some characteristics in 2D-ST imaging help to differentiate TS from anterior myocardium infarction (AMI): (i) radial strain is reduced along the entire mid LV circumference but predominantly reduced in the anterior and anteroseptal wall in AMI; (ii) the average longitudinal strain is significantly lower in TS compared with AMI in midventricular and apical segments predominantly due to lower strain values in inferior, posterior and lateral segments; (iii) ejection fraction and global strain are significantly lower in TS compared with AMI [49].

Cardiac magnetic resonance imaging (CMR) has an important role in patients with Takotsubo and should be performed in stable patients in the subacute phase. The classic criteria of TS in CMR include cine SPSS with regional wall motion abnormalities, most frequently involving the apex; high T2 signal intensity (oedema) and acute absence of late gadolinium enhancement (LGE). If present, acutely patchy LGE usually resolves at follow-up [50]. LGE is useful in the differential diagnosis of TS from myocarditis and myocardial infarction (MI). In myocarditis, we show the presence of epicardial or 'patchy' LGE, and subendocardial or transmural LGE corresponding to a vascular territory is present in MI [50]. Figure 3 presents a typical case of TS.

New sequences in CMR, such as T1 and T2 mapping, are being studied in TS patients. Some studies showed that T1 mapping is superior to conventional T2-weighed imaging (T2WI) for detecting myocardial oedema. Patients with TS present higher native T1 values than control patients, and this feature is negatively associated with LVEF [51]. Native T1 and ECV mapping outperformed T2WI with superior sensitivity and excellent specificity in detecting changes in reversible myocardium in TS. In follow-up, native T1 and ECV of the entire heart also decreased significantly but did not normalize despite LVEF recovery, suggesting that the inflammatory process is not completely resolved [51, 52].

Several cardiac abnormalities may result from cancer or its treatment that promote a CMR evaluation. Cancer treatment with anthracycline and trastuzumab commonly results in the reduction in LVEF due to direct cardiotoxicity. However, in these patients, other aetiologies may be responsible for the reduction of the LVEF, such as TS, myocarditis, myocardium infarction, sepsis and infiltrative disorder. CMR may help to

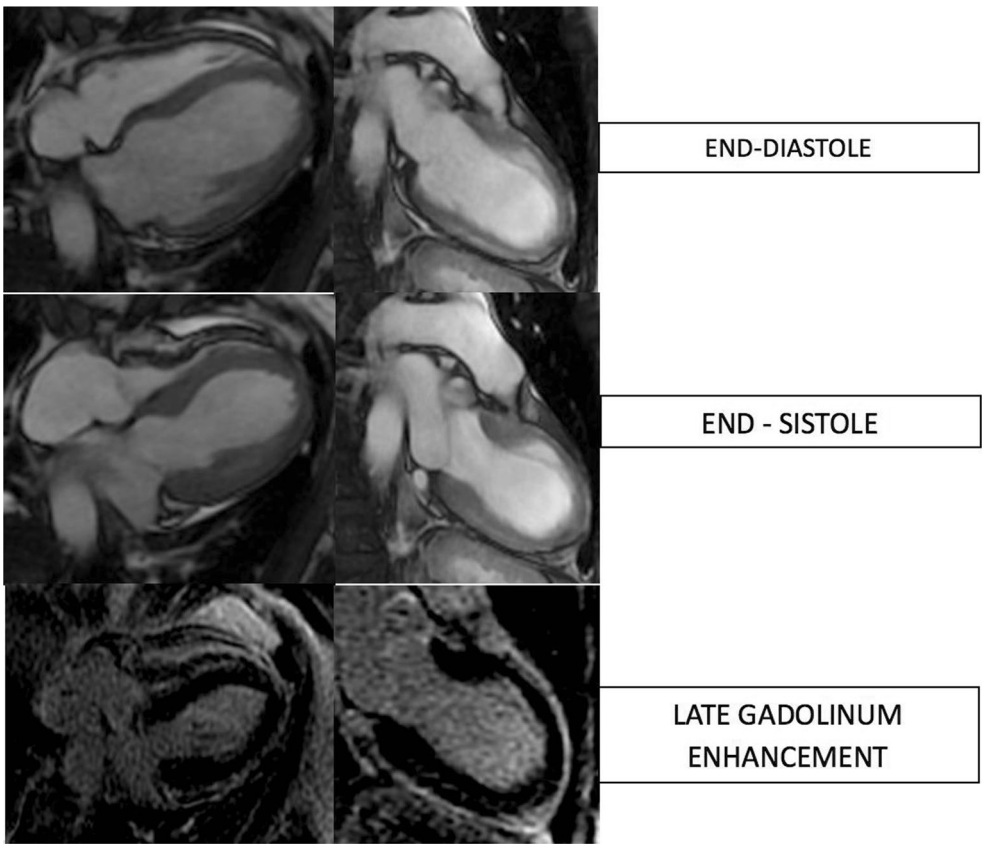

Fig. 3 Image of cardiac resonance of a patient at 70-year-old, woman, diagnosed with melanoma with pulmonary metastasis who initiated chemotherapy with cobimetinib and vemurafenib. After 4 days of the beginning of the chemotherapy, she presented to the emergency room with typical chest pain. There were ischemic electrocardiographic changes and an increase in the measurement of biomarkers of cardiomyocyte injury. Echocardiography showed moderate systolic dysfunction (LVEF 40%) due to apical and midventricular LV dysfunction. Invasive coronary angiography showed no artery stenosis. Cardiac magnetic resonance imaging confirmed the diagnosis. LVEF = left ventricle ejection fraction

differentiate typical cardiotoxicity from these other aetiologies, including TS [32, 50]. In addition, CMR may be used to differentiate the aetiology of a newly identified abnormal myocardial mass, evaluate a pericardial disease process or determine the cause of a valve leaflet abnormality during the same examination when LVEF is measured [50].

Performing urgent coronary angiography, including left ventriculography, is essential to detect TS and to differentiate it from ACS because patients with TS have no coronary culprit lesion to explain the entire left ventricular wall motion abnormality observed in TS [53]. Coronary computed tomography angiography (CCTA) may be considered in stable cases, particularly if the patient is pain free and cardiac imaging (e.g. echocardiography) shows typical features of TS [54].

Treatment

The initial step in the management of Takotsubo syndrome is confirmation of diagnosis. As the initial symptoms are very similar to those of ACS, TS should be considered as a differential diagnosis. Given the high risk of complications, all patients with TS should be admitted to a coronary care unit or high-dependency unit with ECG monitoring for the first 24 h while the investigations and risk stratification are completed [3].

Proper investigations for predisposing diseases, including appropriate management in addition to treatment of TS, might have an impact on the prognosis and in preventing TS recurrence [53].

In mild cases with a LVEF > 45% and without complications, patients can be assessed for hospital discharge, and indications for antiplatelet agents and statins should be reviewed according to lipid profile, coronary angiography and coronary computed tomography angiography results. If LVEF is 35–45%, conventional treatment with angiotensin-converting enzymes (ACEs) and/or angiotensin receptor blockers, beta-blockers and diuretics is often initiated [55].

In patients with haemodynamic left ventricular outflow tract obstruction LVOTO (> 40 mmHg and systolic blood pressure < 110 mmHg), treatment with a beta-blocker or selective alpha1-agonist (e.g. phenylephrine) should be considered [3].

When patients developed cardiogenic shock with significant hypotension, an important step in treatment is to detect whether the hypotension is caused by LVOTO or by primary pump failure [56]. If the diagnosis of LVOTO is confirmed, the suggested treatment is intravenous fluid and parenteral beta-blockers, which increases cardiac filling and suppresses basal hypercontractility, thereby reducing LVOTO [3].

In more severe cases of cardiogenic shock with progressive end-organ dysfunction, avoidance or withdrawal of exogenous catecholamines is recommended, as these agents probably exacerbate or prolong the acute phase. Treatment options include mechanical support for acute cardiogenic shock, such as temporary LV assist devices (LVADs) and extracorporeal membrane oxygenation (ECMO) [3]. Non-catecholamine inotropics, such as levosimendan, may also be considered in primary pump failure in TS, but catecholamine-based inotropics should be avoided [57]. Vasopressin probably might be superior to catecholamines as a vasopressor.

Considering the recent neutral data from the IABP-SHOCK II trial and the fact that intra-aortic balloon counterpulsation (IABP) may worsen dynamic LVOTO, the consensus viewpoint is to avoid the use of IABP in Takotsubo syndrome patients [3].

Thromboembolism is a complication in 4% of TS patients. Left ventricular apical thrombosis may occur due to reversible regional wall motion abnormalities of the left ventricle in the apical segment. Low blood flow within the apical segment is the presumed cause of apical thrombosis. The use of unfractionated heparin or warfarin should be evaluated according to the risk of bleeding [53].

There is no clear consensus in the literature regarding the maintenance of TS therapy in long-term follow-up. Beta-blocker therapy after hospital discharge does not appear to prevent recurrence. ACEi or ARB seems to reduce the recurrence, but more definite studies are needed to better elucidate the role of these medications in TS [41]. Another challenge in these patients involves the optimal time to restart oncologic therapy. Giza et al. showed that the mean time to restart oncologic treatment was approximately 20 days after the cardiac event, as LVEF is typically recovered at this time [12]. If TS is directly related to chemotherapy (acting as a trigger), there is a predisposition to interrupt the drug, which may represent another negative factor in the survival of these patients.

Prognosis and follow-up

Cancer patients typically present a higher incidence of in-hospital complications and worse prognosis [8, 22]. Joy et al. showed that in-hospital complications that require a higher level of care, such as tracheostomy and mechanical ventilation and mortality, were also higher in TS patients with cancer compared with those without cancer [16]. The estimated in-hospital mortality rate in patients with TS in the general population ranges from 4.5% to 5.6%, while in-hospital mortality is approximately 12.8% in cancer patients [16]. Additionally, cancer patients had a significantly longer length of stay (7 vs. 4 days, $p < 0.0001$) and total charges ($29,291 vs. $36,231, $p < 0.0001$) compared with those without malignancy [16].

Girardey et al. showed a higher overall mortality and a higher cardiovascular mortality during the follow-up of 1000 days in these patients compared with individuals without tumours [13]. Sattler et al. observed that the presence of cancer was related to worse outcome during the follow-up of 4 years with a reduction of general survival and event-free survival in these individuals [11]. Long-term mortality was higher in TS patients (39% vs. 21%; HR 1.67, 95% CI 1.00–2.80; $p = 0.05$) [25].

Because TS mimics the clinic presentation of acute coronary syndrome (ACS), early identification of this disease is extremely relevant, especially given that ACS treatment typically involves the use of drugs that have bleeding potential as its adverse effects, such as heparin and antiplatelet agents. Mortality is higher in cancer patients with TS compared with cancer patients with ACS. In TS patients, death mainly occurs via a non-cardiac cause. However, in the ACS group, cardiac death is mainly noted consistent with the prevalence of classical risk factors for cardiovascular disease in this group. The elevated prevalence of several known factors of worse outcome in TS, such as atrial fibrillation, thromboembolic events or QT prolongation, could explain the high mortality rates [24].

It is important to mention that due to the high prevalence of cancer in individuals with a diagnosis of Takotsubo syndrome, some authors currently suggest that screening for malignancy should be performed in patients with TS with no defined aetiology [11]. It is necessary to better investigate the association of these diseases and the best behaviour to be adopted in this scenario, taking into account the severity of these patients.

Takotsubo and pheochromocytoma or paraganglioma tumours

Some tumours, such as pheochromocytoma and paraganglioma, which cause hypercatecholaminaemia, can be triggers of TS. Pheochromocytoma is a catecholamine-secreting tumour that arises from chromaffin tissue of the sympathetic nervous system [58]. Catecholamines play an important role in the pathophysiology of TS, and wall contractile abnormalities may result from the direct effects of catecholamines on cardiomyocytes.

Endomyocardial biopsies reveal occasional contraction band necrosis associated with hypercontracted sarcomeres, dense eosinophilic transverse bands and interstitial mononuclear inflammation as a reflection of myocyte injury. Catecholamines can decrease myocyte viability through cyclic adenosine monophosphate (cAMP)-mediated Ca2b overload as noted in TS [6]. In TS, excessive catecholamine stimulation induces reversible Gs to Gi intracellular stimulation of β2-receptors more prominently in the apex, leading to the transient negative inotropism and hypokinesis, which readily reverses to Gs signalling with decreased stimulation [59].

In our review, we identified 87 articles among 433 articles (Fig. 1) that reported an association between Takotsubo and pheochromocytoma or paraganglioma tumours. The majority were case reports. We identified five original articles (Table 4). These studies showed a high prevalence of TS in patients with pheochromocytoma (Pheo) [18–21]. Pheo-TS was characterized by high complication rates. Two-thirds of Pheo-TS patients developed some type of complications, and almost 1/3 of patients had multiple complications. The complication rates in Pheo-TS were significantly higher than those in patients without Pheo [19].

Given the strong association of Pheo and TS, some authors suggest that pheochromocytoma is a TS-like myocardial dysfunction. The Japanese diagnostic criteria of TS excluded Pheo as a part of TS. Pheochromocytoma is also included as a secondary cause of TS in the diagnostic criteria of the HFA of the ESC [6]. Other authors showed that the TS is the most common type of cardiomyopathy in Pheo patients, but they demonstrated that pheochromocytoma may also present as dilated cardiomyopathy, hypertrophic cardiomyopathy and myocarditis [20, 59]. Pheochromocytoma should be considered in the evaluation of cardiomyopathy even in the absence of symptoms of catecholamine excess. Only 4% in this cohort presented with the classic triad of headaches, palpitations and diaphoresis [59].

The treatment of TS in pheochromocytoma patients includes tumour resection. This procedure was associated with improvement in 96% of cases. Lack of surgery was associated with death, cardiac transplantation or overall serious adverse event [59]. The recurrence of TS is elevated in pheochromocytoma patients and ranges from 14% to 18% of cases [18, 19].

Conclusion

The association between cancer and Takotsubo syndrome was recently recognized and should be considered a severe disease with worse outcomes. The available evidence shows that patients with cancer presenting TS develop more complications and have worse prognosis compared with patients without cancer. Diagnosis and early therapy are essential to achieve better results in these patients.

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