Cardiovascular Pathology 65 (2023) 107543

Contents lists available at ScienceDirect

Cardiovascular Pathology

journal homepage: www.elsevier.com/locate/carpath

Postmortem diagnosis of Takotsubo syndrome on autoptic findings: is it reliable? A systematic review ☆

Simone Grassi [1,2,†], Oscar Campuzano [3,†], Francesca Cazzato [2,*], Mònica Coll [3], Alessandra Puggioni [1], Massimo Zedda [2], Vincenzo Arena [4], Anna Iglesias [3], Georgia Sarquella-Brugada [5], Vilma Pinchi [1], Ramon Brugada [3,6,‡], Antonio Oliva [2,‡]

[1] Department of Health Sciences, Section of Forensic Medical Sciences, University of Florence, largo Brambilla 3, 50134, Florence, Italy
[2] Department of Health Surveillance and Bioethics, Section of Legal Medicine, Fondazione Policlinico A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, 00168 Rome, Italy
[3] Cardiovascular Genetics Center, University of Girona-IDIBGI, 17190 Girona, Spain
[4] Institute of Pathological Anatomy, School of Medicine, Catholic University, 00168 Rome, Italy
[5] Pediatric Arrhythmias, Inherited Cardiac Diseases and Sudden Death Unit, Cardiology Department, Sant Joan de Déu Hospital de Barcelona, 08950 Barcelona, Spain
[6] Centro de Investigación Biomédica en Red. Enfermedades Cardiovasculares (CIBERCV), 28029 Madrid, Spain

ARTICLE INFO

Article history:
Received 3 March 2023
Revised 3 May 2023
Accepted 4 May 2023

Keywords:
Sudden cardiac death
Takotsubo syndrome
Takotsubo cardiomyopathy histopathology
Forensic pathology

ABSTRACT

Takotsubo syndrome (TTS) is a cardiac syndrome characterized by transient left ventricular systolic dysfunction in the absence of significant obstructive coronary artery disease. At the autopsy, its diagnosis is often challenging, since it is generally thought that it relates to no characteristic macroscopic or microscopic findings. In order to verify this last statement, we performed a systematic review of the literature following Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) criteria. To the best of our knowledge, it is the first systematic review addressing this issue. We identified recurring but not pathognomonic (microscopic) features of TTS: contraction band necrosis and non-specific inflammatory changes (e.g., interstitial infiltrates of mononuclear lymphocytes and macrophages) typically in the absence of microscopic findings typical of acute myocardial infarction. In cases of TTS-related sudden death, careful evaluation of anamnesis, autopsy data and post-mortem genetic results (to exclude other causes) should be considered to overcome the complexity of these cases.

1. Introduction

Takotsubo syndrome (TTS) (ORPHA:66529) is an increasingly recognized cardiac syndrome characterized by transient left ventricular systolic dysfunction in the absence of significant obstructive coronary artery disease. Typically, cardiac dysfunction is identified as “apical ballooning” or focal wall motion abnormalities (Fig. 1); actually, the term Takotsubo was taken from the Japanese word meaning “octopus trap” due to the characteristic apical ballooning appearance of the left ventricle.

TTS was firstly reported in Japan in 1991 [2], but even before this, others reported people died of acute intense stress without evidence of any physical injury. It is also known as Takotsubo cardiomyopathy (TCM), stress-induced cardiomyopathy or broken heart syndrome. TTS is mainly caused by emotional and/or physical catecholaminergic triggers thus suggesting an increased sympathetic activity. However, recent studies suggest that there is an interplay between inflammation, genetics, and oxidative status which might explain susceptibility to the condition [3]. It was generally considered a benign condition but is increasingly recognized that TTS is not a benign condition and can be associated with severe clinical complications such as heart failure, thromboembolic events, cardiogenic shock, and sudden cardiac death (SCD) [4,5]. TTS mainly affects women older than 50 years, particularly those postmenopausal, who have a 5-fold risk compared to younger women and 10 times greater than men [6]. Despite this fact, men have higher morbidity and mortality rates [7]. The in-hospital

☆ This work has been supported by Fondi di Ateneo, Linea D.1, Università Cattolica del Sacro Cuore.
* Correspondence: Francesca Cazzato, Largo Francesco Vito 1, 00168, Rome, Italy.
E-mail address: francescacazzato993@gmail.com (F. Cazzato).
† S.G. and O.C. should be considered co-first authors.
‡ R.B. and A.O. should be considered co-senior authors.

https://doi.org/10.1016/j.carpath.2023.107543
1054-8807/

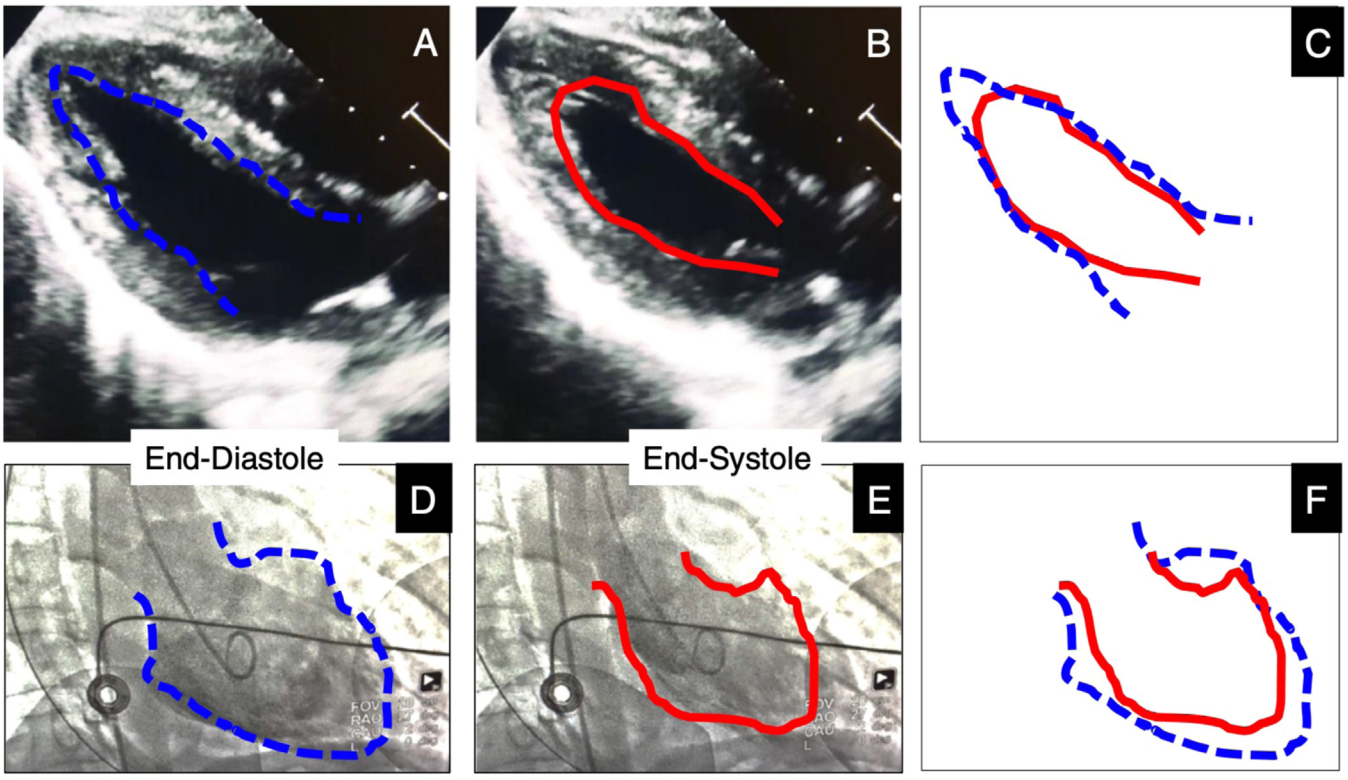

Fig. 1. Akinesis of the midventricular segments in a noncoronary distribution: transthoracic echocardiogram parasternal long-axis view (A and B) with reconstruction (C); left ventricular contrast angiography right oblique view (D and E), with reconstruction (F). Reprinted from Cardiovascular Pathology, Del Buono et al. [1].

mortality rate is about 4.5% [8,9], while long-term mortality data during follow-up are heterogeneous (ranging from 5% to 17%) [10]. Some recent studies suggest that the prognosis of TTS patients is similar to that of patients with myocardial infarction, but other Authors found no significant difference in mortality between patients with TTS and age- and sex-matched people [11,12]. Moreover, despite being uncommon, TTS has been described in children, including premature neonates [13]. TTS accounts for about 2%-3% of all patients presenting with acute chest pain, ischemic electrocardiogram (ECG) changes and slight elevation of cardiac enzymes [5,14], although it may be underdiagnosed especially in patients who have coexisting coronary artery disease (CAD) [15]. The incidence of the disease is increasing due to improved clinical awareness and widespread access to coronary angiography (CAG) [16,17]. Nowadays, despite pathophysiological mechanisms underlying TTS appearing to correlate with catecholamine excess in the setting of stressful triggers, definite mechanisms underlying TTS have not been fully clarified so far and diagnosis is often challenging, possibly leading to misdiagnoses or missed diagnoses [4,5]. Today TTS is commonly divided into 2 clinical subtypes: primary TTS is a leading cause of hospital admission, commonly triggered by psychosocial stress, although emotional stress may not be identifiable in some cases; secondary TTS develops among patients already admitted to hospitals due to other various conditions, and may also involve drug-induced TTS [18,19] Furthermore, there is another clinical classification which subdivides TTS into apical, mid-ventricular, basal, focal, and biventricular based on the wall motion abnormality location [20].

Focusing on tissutal alterations helping to make a differential diagnosis at autopsy, no conclusive pathognomonic/specific macroscopic and microscopic features of TTS are reported in the scientific literature so far. There are few reports on the pathomorphological features of the heart, which means that more research is needed to look more closely at the pathophysiology of TTS and to identify independent predictors of fatal complications. Nowadays, at the autopsy, TTS frequently shows ambiguous histopathological features and may also co-exist with coronary artery disease (CAD) in a small proportion of cases, thus representing a challenging diagnosis [21,22]. In recent studies, some microscopic alterations have been reported as myocardial thinning, Lewy body-like inclusions, interstitial edema with the accumulation of inflammatory cells, and myocardial necrosis [23]. In this review, given the common clinical features between TTS and other cardiac diseases (such as CAD), we sought to evaluate the reliability of post-mortem diagnosis. To achieve this, we performed a systematic review focused on the reported macroscopic and microscopic cardiac findings, observed at autopsies of people diagnosed with TTS.

2. Material and methods

We performed a systematic literature search according to the current Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) criteria (Fig. 2). We searched PubMed and Scopus databases for papers published between January 1, 2004 and January 5, 2023. We used a search string (restricted to the terms in the paper titles and abstracts) in which, using the Boolean operator "AND," we combined the terms ("Takotsubo or Broken heart syndrome") with the terms ("sudden cardiac death or died or cardiac arrest or death") and with the terms ("genetic or histology or structural alternations or autopsy or findings or finding or biopsy or histopathology"). We developed and applied one search strategy for each database. Two authors independently performed a preliminary search and retrieved and selected articles that fulfilled the inclusion criteria: research studies written in English that evaluated a possible correlation between TTS and certain structural cardiac alterations.

Our preliminary research identified 195 papers, 106 through Pubmed and 89 through Scopus. After the removal of 73 dupli-

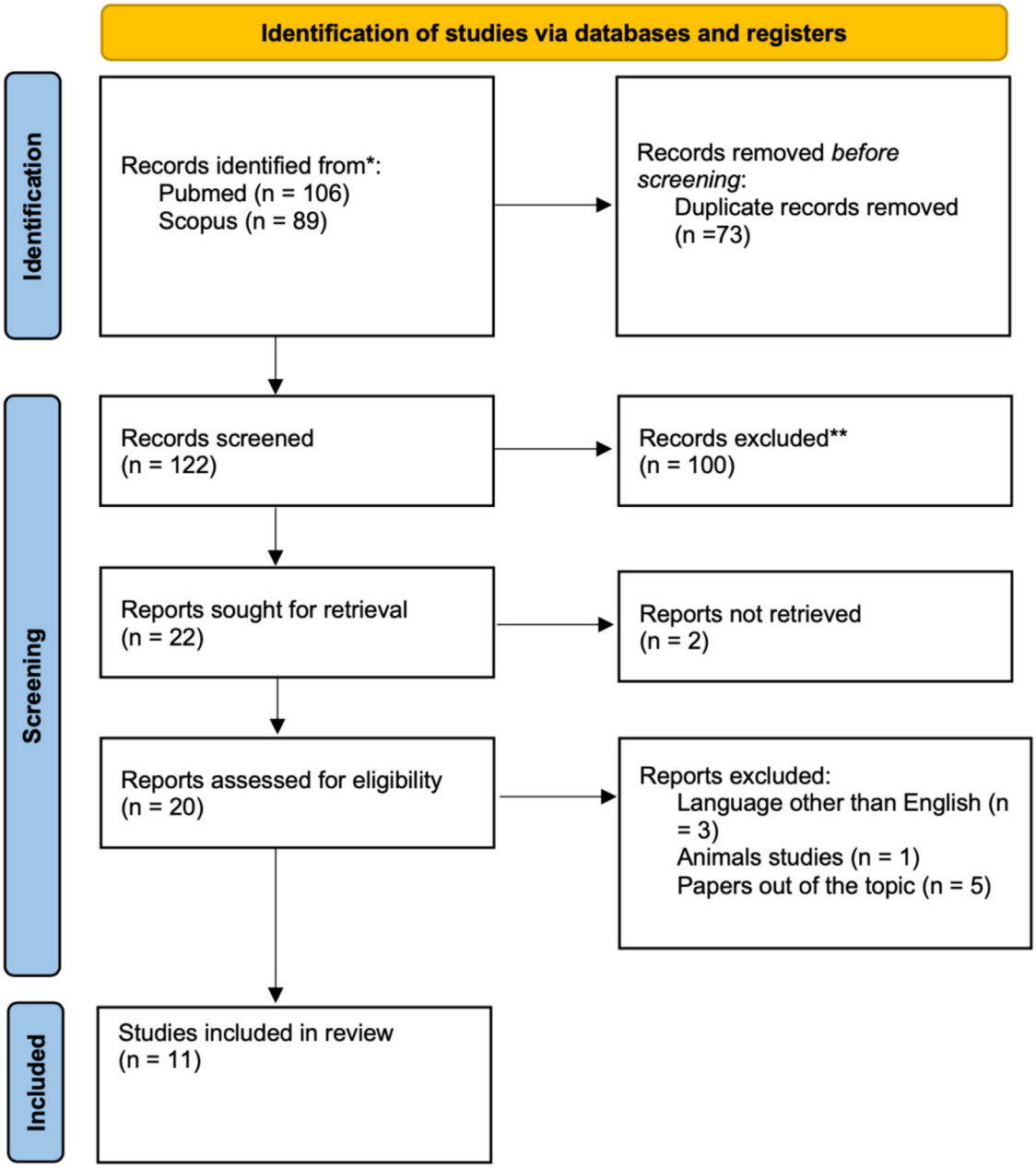

Fig. 2. PRISMA flow diagram followed in this review.

cates, 100 papers were excluded as they did not meet the inclusion criteria based on the title and abstract analyses. Of the 22 articles remaining, 2 were excluded due to the unavailability of the full text. Hence, a total of 20 papers were assessed for eligibility. Full texts of reviews, experimental studies in animal models, conference articles, articles that did not focus on macroscopic and microscopic cardiac findings in TTS, and articles that were not published in English were removed from the pool of eligible papers. Following the exclusion criteria, 11 eligible publications were included in our analysis and were critically reviewed by 3 investigators who extracted data relevant to the purpose of the present study. All authors agreed on the final data included in our study. Relevant information of eligible papers was summarized in Table 1 considering these variables: number of the reference, personal information, main macroscopic/microscopic findings, technique used for microscopic analysis, and whether toxicology/genetic testing was performed.

3. Results

3.1. Macroscopic and microscopic findings of TTS cases found at autopsy

Bottari et al. [24] reported the sudden death (SD) of an apparently healthy 75-year-old woman who died of TTS after a robbery. The autopsy showed a heart (weight: 390 g) without significant macroscopic anomalies (i.e., mild left ventricular dilatation and non-occlusive atherosclerotic plaques in the coronary arteries). At the microscopic examination, diffuse areas of interstitial edema with myocardial cell fragmentation and a focal polymorphonuclear leukocyte infiltrate were observed. Moreover, the left ventricle wall presented mild interstitial and subendocardial fibrosis and some areas of wavy fibers and contraction band necrosis.

Del Buono et al. [1] reported an autopsy of a 23-year-old woman cannabis chronic consumer, revealing the presence of con-

Table 1
Summary of the literature review regarding autopsy samples of TTS.

Reference	Gender	Age	Heart weight	Macroscopic findings	Microscopic findings	Technique of microscopy	Toxicology testing	Genetic testing
Bottari [24]	Female	75	390 g	Mild left ventricular dilatation, non-occlusive atherosclerotic plaques in the coronary arteries	*Fragmentatio cordis* with focal polymorphonuclear leukocyte infiltrate, wavy fibers, contraction band necrosis, interstitial and subendocardial fibrosis	Hematoxylin-eosin	No	No
Del Buono [1]	Female	23	NA	Sub-acute subendocardial hemorrhages	Inflammatory infiltrates, contraction band formations, myocardial necrosis	Hematoxylin-eosin	Yes (negative)	No
Iskander [25]	Female	77	380 g	Transmural hemorrhage with a slit-like rupture on the antero-apical surface extended into the papillary muscles, hypertrophy of the left ventricle, patent coronary arteries	Hemorrhagic foci, neutrophilic infiltration, hypereosinophilic contraction band necrosis	Hematoxylin-eosin	No	No
Jan [26]	Males and Females	4–69 months	NA	NA	Wavy myocytes, coagulative myocytolysis in the left ventricle	Hematoxylin and eosin stain, Elastic tissue-Masson technique, in situ terminal deoxyribonucleotidyl transferase-mediated dUTP	No	No
Kinbara [27]	Male	69	NA	Hypertrophic left ventricle, diffuse circumferential necrosis of the left ventricle	Myocardial necrosis, contraction band necrosis	Hematoxylin-eosin	No	No
Kirigaya [28]	Male	56	NA	Patent coronary arteries	Diffuse contraction band necrosis, myocardial atrophy	Hematoxylin-eosin, Phosphotungstic acid hematoxylin stain	No	No
Mitchell [29]	Female	82	360 g	Slit-like rupture of the base of the right ventricle, epicardial hemorrhage, patent coronary arteries	Contraction band necrosis in the rupture site with polymorphonuclear leukocyte infiltrates; patchy mononuclear cell infiltrates of lymphocytes and macrophages, and rare polymorphonuclear leukocytes, mast cells and eosinophils	Hematoxylin-eosin	No	No
Mizutani [30]	Female	91	360 g	Dilation of the left ventricle in the mid-basal segment and thinning of the mid-apical segment, patent coronary arteries	Wavy of myocytes, interstitial fibrosis, hemorrhage, neutrophil infiltration, contraction band necrosis on the posterior to inferior wall of the left ventricle	Hematoxylin-eosin, Masson trichrome staining	No	No
Toni [31]	Female	65	480 g	Apical biventricular ballooning, moderate left ventricle concentric hypertrophy, patent coronary arteries	Scattered contraction bands necrosis, mild myocyte hypertrophy in the left ventricle	Hematoxylin-eosin	Yes (negative)	No
Tran [32]	Female	34	326 g	Dilatation of both ventricles at the base of the heart	Wavy myocytes, contraction bands, focal subendocardial myocytolysis, inflammatory cells, focal perivascular fibrosis in the left ventricle; focal subendocardial fibrosis and mild myocyte hypertrophy in the right ventricle	Hematoxylin-eosin	Yes (therapeutic concentration of an anti-inflammatory drug)	No
Tsunoda [33]	Female	74	465 g	Transmural myocardial necrotic zone with a small thrombus inside the left ventricular free wall rupture, obstructive lesion in the diagonal branch of the coronary arteries	Inflammatory cell infiltrations, interstitial fibrosis, hemorrhage, coagulation necrosis; ostial lesion with stenosis due to plaque, dissection, and thrombus	Hematoxylin-eosin	No	No

NA, not available; No, toxicology/genetic testing not performed; Yes, toxicology/genetic testing performed; Negative, toxicology/genetic testing negative.

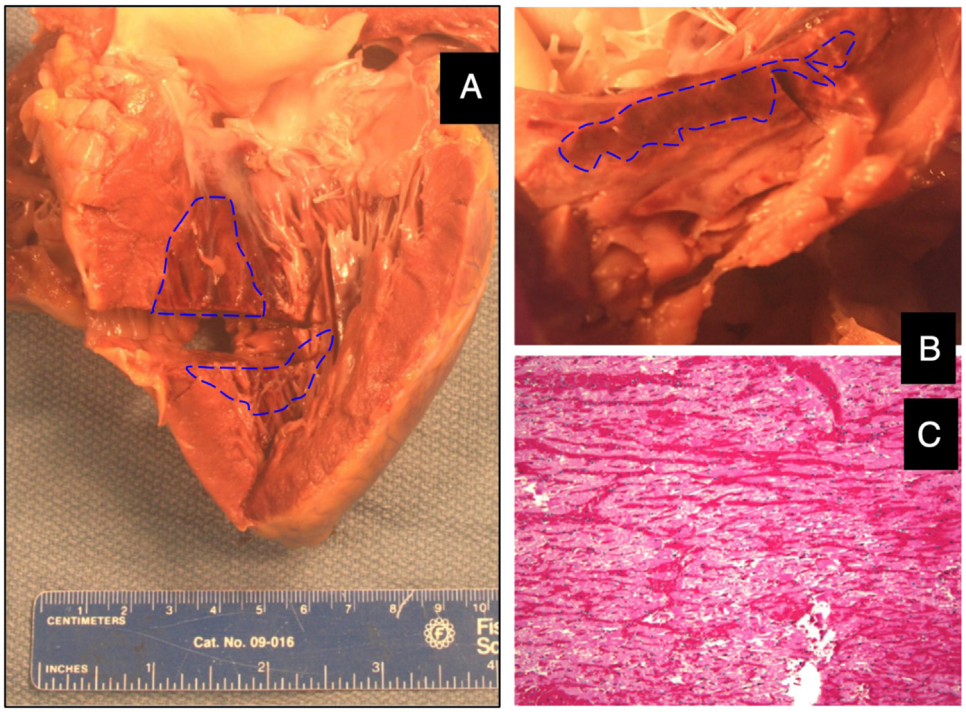

Fig. 3. (A) areas of subendocardial hemorrhages in the midventricular anterior wall and papillary muscle at the gross examination; (B) macroscopic enlargement secondary to the subendocardial hemorrhage; (C) microscopic subendocardial hemorrhage (hematoxylin and eosin). Reprinted from Cardiovascular Pathology, Del Buono et al. [1].

traction band formations, myocardial necrosis, inflammatory infiltrates, and subendocardial hemorrhages (described as sub-acute reportedly according to the characteristics of the inflammatory response, not better specified) at histopathological analysis (Fig. 3).

Iskander et al. [25] reported a SD due to TTS in a 77-year-old woman who presented a heart (weight: 380 g) with an area of transmural hemorrhage and a with a slit-like rupture on the antero-apical surface extended into the papillary muscles. Moreover, hemorrhagic foci with polymorphonuclear cells infiltrates and hypereosinophilic contraction band necrosis were observed microscopically.

Jan et al. [26] reported 7 children died of TTS while affected by Enterovirus 71 infection. The macroscopic cardiac findings were not available. Microscopically, degeneration and wavering of the myocardial fibers with coagulative myocytolysis and different degrees of cardiomyocyte apoptosis were observed, especially in the left ventricle. Real-time polymerase chain reaction showed no evidence of viral myocarditis.

Kinbara et al. [27] reported the autopsy findings of a 69-year-old man died of TTS immediately after pacemaker implantation. Macroscopically, slight hypertrophy of the left ventricle together with diffuse myocardial necrosis along the entire circumference and in all layers of this ventricle was observed. Focused on histopathological alterations, myocardial necrosis and contraction band necrosis were found.

Kirigaya et al. [28] reported the case of a 56-year-old man died of TTS after refractory hypoglycemia. The autopsy revealed no macroscopic anomalies. Histopathological examination of the heart showed myocardial atrophy and contraction band necrosis in both ventricles.

Mitchell et al. [29] reported the case of an 82-year-old woman who died of TTS and secondary myocardial rupture after elective craniotomy for resection of a craniopharyngioma. At gross examination, the heart (weight: 360 g) with myocardial rupture at an unusual site (at the base of the right ventricle) and an epicardial hemorrhage was found. In addition, contraction band necrosis, interstitial edema with mononuclear cell infiltrates of lymphocytes and macrophages, and rare polymorphonuclear leukocytes, mast cells, and eosinophils involving both ventricles were detected at microscopic analysis.

Mizutani et al. [30] reported the case of a 91-year-old woman who died after the recurrent episode of TTS. At autopsy, the heart (weight: 360g) showed dilation of the left ventricle in the mid-basal segment and thinning of the mid-apical segment. At the histopathological examination, interstitial fibrosis, hemorrhage, neutrophil infiltration, and contraction band necrosis on the posterior to inferior wall of the left ventricle were observed.

Toni et al. [31] described the SD of a 65-year-old woman after local anesthesia during a minor oral surgery with a clinical history of recurrent TTS. Post-mortem gross examination showed heart (weight: 480 g) with apical biventricular ballooning and moderate left ventricular concentric hypertrophy, while scattered contraction bands necrosis and mild myocyte hypertrophy in the left ventricle were observed microscopically.

Tran et al. [32] reported the case of a 34-year-old woman, who died of inverted TTS. At gross examination, dilatation of both ventricles at the base of the heart (weight: 326 g) was observed. Microscopically, wavy myocytes, contraction bands, focal subendocardial myocytolysis, inflammatory cells, focal perivascular fibrosis were detected in the left ventricle. In addition, focal subendocardial fibrosis and mild myocyte hypertrophy were found in the right ventricle.

Tsunoda et al. [33] reported a case of a 74-year-old woman with left ventricular free wall rupture associated with a combination of acute myocardial infarction and TTS. The autopsy revealed hemopericardium and a rupture site on the left ventricle of the heart (weight: 465 g) with a transmural myocardial necrotic zone and a small mural thrombus inside the necrotic wall. Moreover, an obstructive lesion in the diagonal branch of the coronary arteries was observed macroscopically. At histopathological examination, inflammatory cell infiltrations, interstitial fibrosis, hemorrhage, and coagulation necrosis were observed at the rupture site

and an ostial lesion with stenosis due to plaque, dissection, and thrombus was found.

4. Discussion

Recent several studies have shown that TTS is associated with significant short- and long-term morbidity and mortality [5]. The prevalence of TTS among SCD cases is not reported probably because it is included in the generic group of cardiomyopathies and because it is still an underestimated disease. SCD is a relatively common condition, and it may also show no or only ambiguous findings at autopsy. For these reasons, clinical and forensic autopsies in cases of TTS might be challenging. Our systematic review focuses on post-mortem cases of TTS and shows that the main issues complicating the postmortem diagnostic process are the absence of pathognomonic/specific features of TTS detectable at autopsy. Thus, without a clinical suspicion or an ante-mortem diagnosis it could be difficult to distinguish it from other causes of SCD [34].

In most of the cases analyzed, macroscopic structural changes were absent or slight non-specific structural anomalies were reported (e.g., mild ventricular dilatation/hypertrophy) [24,27,28,30–32]. However, some structural anomalies at gross examination of the heart have been observed in other TTS patients. Thus, Mizutani et al. [30] and Toni et al. [31] reported that at autopsy, the heart had a similar shape (Takotsubo-like) to that observed ante-mortem observed at clinical examination by echocardiography. Both victims were suffering from recurrent TTS. Therefore, it can be assumed that in such cases the repeated myocardial damage becomes progressively irreversible and may eventually lead to fatal heart failure macroscopically detectable at autopsy. In addition, a slit-like rupture in the left ventricular free wall was reported in 2 cases [25,33], and in one case this finding was observed at the base of the right ventricle (an unusual site) [29]. Cardiac ruptures are life-threatening mechanical complications of TTS, sharing the same risk factors with acute myocardial infarction (MI) (e.g., female gender, advanced age, and hypertension) [25,35]. Since ventricular free wall rupture is more common in the apical form of TTS, it has been hypothesized that these patients have a poorer prognosis than those with mid-ventricular and basal forms of TTS. At this regard, severe forms of TTS, such as those resulting in heart wall ruptures, may be associated with different types of hemorrhages (i.e., subendocardial, subepicardial, or transmural) [1,36].

In most of the patients studied, the coronary arteries were patent. However, at clinical examination, differential diagnosis with acute MI can be challenging when underlying CAD coexists. At postmortem investigation, the suspicion of acute MI at gross examination is usually later ruled out by histopathological analysis of coronary arteries (i.e., absence of complicated atherosclerotic plaques and an intact muscular layer) [24]. However, Tsunoda et al. [33] reported a rare case in which TTS and acute MI are supposed to coexist. Even though some guidelines suggest that an obstructive epicardial CAD should be excluded in the diagnosis of TTS, the authors hypothesized that stress-related myocardial damage is one of the mechanisms by which these diseases might coexist [5,33,37].

Hence, microscopic analysis can be considered the main post-mortem diagnostic tool. Our comprehensive analysis identified recurring but not pathognomonic microscopic features of TTS, including some inflammatory changes (e.g., interstitial infiltrates of mononuclear lymphocytes and macrophages) and contraction bands with or without myocardial necrosis. These histopathological features -especially contraction band necrosis (CBN) (Fig. 4) - resemble those usually observed in clinical situations characterized by catecholamine excess, finally resulting in a “catecholamine-induced cardiotoxicity” [25,27].

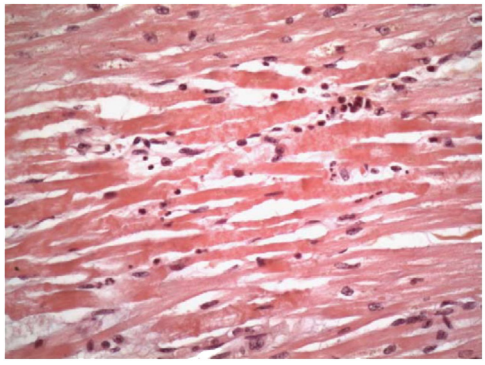

Fig. 4. Area of contraction band necrosis (hematoxylin and eosin, 200x magnification). Reprinted from Cardiovascular Pathology, Maréchaux et al. [38].

At this regard, although pathogenesis of TTS has not been fully elucidated and several hypotheses have been postulated (e.g., multivessel epicardial coronary artery spasm, coronary microvascular impairment and neurogenic stunned myocardium), current evidence suggests myocardial catecholamine toxicity as the main underlying mechanism of the disease [32,39]. This hypothesis implies that similar features could be found in exogenous catecholamines administration or pheochromocytoma. However, to date this topic is still debated and there is no unanimous consensus within the scientific community [40]. For this reason, during the paper’s selection process, we decided to exclude from the eligible papers those characterized by pheochromocytoma detection, according to the most widely diagnostic criteria proposed by the Mayo Clinic [5,21].

Therefore, especially in the absence of macroscopic evidence of obstructive CAD, these microscopic findings should be explored by the pathologist, as they may be suggestive of a TTS. Furthermore, histopathologically acute MI differs from TTS by the detection of coagulation necrosis and dense polymorphonuclear infiltrates.

It should be noted that TTS is classified as a chronic disease: thus, irreversible myocardial alterations observed in some cases (e.g., wavy change, thinning, and fibrosis) may result from the recurrence of episodes of TTS, finally exposing the patient to life threating events [30].

Thus, differential diagnosis may be of considerable forensic interest – for example – when a missed diagnosis of TTS is claimed due to medical malpractice [24,39].

The forensic pathologist could be asked to establish whether the cause of death was a condition that the healthcare professionals should have detected [34].

Moreover, of great and challenging forensic interest are SCDs due to TTS occurring after a criminal act (e.g., physical and verbal assault), as the public prosecutor may require the forensic pathologist to establish whether there is a causal relationship between the offender’s criminal action and the fatal event [24].

Although our literature review did not reveal conclusive neither macroscopic nor microscopic findings in TTS patients, the detection of these histopathological changes may help the forensic pathologist in the post-mortem diagnosis of TTS. In these cases, acute MI is still the main differential diagnosis. As mentioned, TTS can also coexist with coronary artery disease (CAD) in a small percentage of cases and the post-mortem differential diagnosis may be even more challenging than the ante-mortem diagnosis. However, in autopsy settings, the macroscopic absence of obstructive CAD, the presence of contraction band necrosis (found in 9 out of 11 cases), the detection of inflammatory changes (e.g., interstitial infiltrates of mononuclear lymphocytes and macrophages) and the absence of microscopic findings typical of acute MI (i.e., coagulation necro-

sis and dense polymorphonuclear infiltrates) might be considered as suggestive of a TTS.

As said in the introduction, TTS is a "regional" disorder in which – in the classical variant – the impairment of contractility is confined in the mid-apical portion, with a hypercontractility of the basal segment. Therefore, it would of great translational value if a correlation between functionally impaired areas and microscopic alterations is found. That being said, the localization of microscopic alterations was not always addressed in the reviewed papers. When discussed, the anomalies were often described as diffuse (without a specific pattern of distribution) in the left ventricle or in both ventricles [26,27,29,32]. At this regard, albeit reporting diffuse alternations, Mizutani et al. [30] described which areas were mainly affected: wavy fibers, thinning of myocardium, interstitial fibrosis, hemorrhages and neutrophil infiltrations were mainly found in the apex and in the anterior-to-lateral wall of the left ventricle, in the interventricular septum and in the right ventricle. Left ventricular involvement is generally predominant or exclusive. Indeed, Bottari et al. [24] reported mild interstitial/subendocardial fibrosis, areas of wavy fibers and contraction band necrosis in the left ventricle's wall. Toni et al. [31] reported scattered contraction bands and mild hypertrophy (without fibrosis) in the left ventricle. Only Tsunoda et al. [33] directly addressed the topic of the comparison between functionally and microscopically alliterated areas. However, their results are of scarce translational value, since the left inferior-posterior wall, that showed akinesis at the ventriculography, presented no microscopic alterations.

Furthermore, in cadavers with a conclusive ante-mortem diagnosis of TTS, performing a "molecular autopsy" should be highly recommended for future genotype-phenotype correlations. Indeed, recently, it has been hypothesized that the genetic predisposition, may play a causal role in the development of TTS [41]. However, to date, a comprehensive investigation of genetic factors significantly associated with TTS is lacking [41] and also in the current study none of the patients had undergone post-mortem genetic testing [34,42]. Therefore, further research on genetic analysis of both living and deceased patients is needed to ensure maximum diagnostic yield. When a definitive ante-mortem diagnosis has not been made, identification of a TTS at autopsy may be the only opportunity to detect it.

5. Conclusions

TTS is a rare entity that gained increased recognition throughout the medical community in last years. Despite being considered as a benign disease, TTS leads to an unfavorable outcome, with up to 17% risk of death due to acute hemodynamic instability and arrhythmic complications. TTS is mainly caused by catecholaminergic situations, despite pathophysiological mechanisms involved in TTS are still not completely understood to date. The diagnosis for both clinicians and pathologist are challenging and should look for signs distinguishing TTS from other entities. Further research studies in large postmortem cohorts are necessary to solve current challenges in forensic field and translate this knowledge into viable approaches for post-mortem diagnosis of TTS.

Author contributions

All authors have contributed equally. All authors have read and agreed to the published version of the manuscript.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Data availability statement

Not applicable.

Declaration of Competing Interest

All authors declare that they have no conflict of interest.

References

[1] Del Buono MG, O'Quinn MP, Garcia P, Gerszten E, Roberts C, Moeller FG, Abbate A. Cardiac arrest due to ventricular fibrillation in a 23-year-old woman with broken heart syndrome. Cardiovasc Pathol 2017;30:78–81. doi:10.1016/j.carpath.2017.06.007.
[2] Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. J Cardiol 1991;21:203–14.
[3] Viceconte N, Petrella G, Pelliccia F, Tanzilli G, Cicero DO. Unraveling pathophysiology of takotsubo syndrome: the emerging role of the oxidative stress's systemic status. J Clin Med 2022;11:7515. doi:10.3390/jcm11247515.
[4] Ghadri J-R, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Templin C. International Expert Consensus Document on Takotsubo Syndrome (Part II): diagnostic workup, outcome, and management. Eur Heart J 2018;39:2047–62. doi:10.1093/eurheartj/ehy077.
[5] Singh T, Khan H, Gamble DT, Scally C, Newby DE, Dawson D. Takotsubo syndrome: pathophysiology, emerging concepts, and clinical implications. Circulation 2022;145:1002–19. doi:10.1161/CIRCULATIONAHA.121.055854.
[6] Deshmukh A, Kumar G, Pant S, Rihal C, Murugiah K, Mehta JL. Prevalence of Takotsubo cardiomyopathy in the United States. Am Heart J 2012;164:66–71.e1. doi:10.1016/j.ahj.2012.03.020.
[7] Abuelazm M, Saleh O, Hassan AR, Ahmad S, Albarakat MM, Paul TK. Sex difference in clinical and management outcomes in patients with Takotsubo syndrome: a systematic review and meta-analysis. Curr Probl Cardiol 2023;48:101545. doi:10.1016/j.cpcardiol.2022.101545.
[8] Singh K, Carson K, Shah R, Sawhney G, Singh B, Parsaik A, Horowitz J. Meta-analysis of clinical correlates of acute mortality in Takotsubo cardiomyopathy. Am J Cardiol 2014;113:1420–8. doi:10.1016/j.amjcard.2014.01.419.
[9] Brinjikji W, El-Sayed AM, Salka S. In-hospital mortality among patients with takotsubo cardiomyopathy: a study of the National Inpatient Sample 2008 to 2009. Am Heart J 2012;164:215–21. doi:10.1016/j.ahj.2012.04.010.
[10] Stiermaier T, Moeller C, Oehler K, Desch S, Graf T, Eitel C, Eitel I. Long-term excess mortality in takotsubo cardiomyopathy: predictors, causes and clinical consequences. Eur J Heart Fail 2016;18:650–6. doi:10.1002/ejhf.494.
[11] Elesber AA, Prasad A, Lennon RJ, Wright RS, Lerman A, Rihal CS. Four-year recurrence rate and prognosis of the Apical Ballooning syndrome. J Am Coll Cardiol 2007;50:448–52. doi:10.1016/j.jacc.2007.03.050.
[12] Butt JH, Bang LE, Rørth R, Schou M, Kristensen SL, Yafasova A, Fosbøl EL. Long-term risk of death and hospitalization in patients with heart failure and takotsubo syndrome: insights from a Nationwide Cohort. J Card Fail 2022;28:1534–44. doi:10.1016/j.cardfail.2022.02.002.
[13] Ghadri J-R, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Templin C. International Expert Consensus Document on Takotsubo syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J 2018;39:2032–46. doi:10.1093/eurheartj/ehy076.
[14] Minhas AS, Hughey AB, Kolias TJ. Nationwide Trends in Reported Incidence of Takotsubo Cardiomyopathy from 2006 to 2012. Am J Cardiol 2015;116:1128–31. doi:10.1016/j.amjcard.2015.06.042.
[15] Napp LC, Cammann VL, Jaguszewski M, Szawan KA, Wischnewsky M, Gili S, Templin C. Coexistence and outcome of coronary artery disease in Takotsubo syndrome. Eur Heart J 2020;41:3255–68. doi:10.1093/eurheartj/ehaa210.
[16] Assad J, Femia G, Pender P, Badie T, Rajaratnam R. Takotsubo syndrome: a review of presentation, diagnosis and management. Clin Med Insights Cardiol 2022;16:117954682110657. doi:10.1177/11795468211065782.
[17] Murugiah K, Wang Y, Desai NR, Spatz ES, Nuti SV, Dreyer RP, Krumholz HM. Trends in short- and long-term outcomes for Takotsubo cardiomyopathy among medicare fee-for-service beneficiaries, 2007 to 2012. JACC Heart Fail 2016;4:197–205. doi:10.1016/j.jchf.2015.09.013.
[18] Kido K, Guglin M. Drug-induced Takotsubo cardiomyopathy. J Cardiovasc Pharmacol Ther 2017;22:552–63. doi:10.1177/1074248417708618.
[19] Núñez-Gil IJ, Almendro-Delia M, Andrés M, Sionis A, Martin A, Bastante T, Barrabés J. Secondary forms of Takotsubo cardiomyopathy: a whole different prognosis. Eur Heart J Acute Cardiovasc Care 2016;5:308–16. doi:10.1177/2048872615589512.
[20] Okura H. Update of takotsubo syndrome in the era of COVID-19. J Cardiol 2021;77:361–9. doi:10.1016/j.jjcc.2020.10.004.
[21] Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 2008;155:408–17. doi:10.1016/j.ahj.2007.11.008.

[22] Madhavan M, Prasad A. Proposed Mayo Clinic criteria for the diagnosis of Tako-Tsubo cardiomyopathy and long-term prognosis. Herz 2010;35:240–4. doi:10.1007/s00059-010-3339-x.
[23] Aoki Y, Kodera S, Watanabe T, Miyauchi Y, Kanda J, Ooe K. Autopsy findings in takotsubo cardiomyopathy with special reference to the autonomic nervous system. Int J Cardiol 2016;203:236–7. doi:10.1016/j.ijcard.2015.10.121.
[24] Bottari G, Trotta S, Marzullo A, Meliota G, Ciccone MM, Solarino B. Sudden cardiac death after robbery: Homicide or natural death? J Forensic Leg Med 2020;75:1–5. doi:10.1016/j.jflm.2020.102057.
[25] Iskander M, Abugroun A, Shehata K, Iskander F, Iskander A. Takotsubo cardiomyopathy-induced cardiac free wall rupture: a case report and review of literature. Cardiol Res 2018;9:244–9. doi:10.14740/cr728w.
[26] Jan S-L, Fu Y-C, Chi C-S, Lee H-F, Huang F-L, Wang C-C, Hwang B. Catecholamine-induced secondary takotsubo syndrome in children with severe enterovirus 71 infection and acute heart failure: a 20-year experience of a single institute. Front Cardiovasc Med 2021;8:1–9. doi:10.3389/fcvm.2021.752232.
[27] Kinbara T, Hayano T, Otani N, Furutani Y, Murakami T, Yano M. An autopsy case of tako-tsubo cardiomyopathy presenting ventricular tachycardia after pacemaker implantation. J Cardiol Cases 2013;8:134–7. doi:10.1016/j.jccase.2013.06.007.
[28] Kirigaya J, Iwahashi N, Tanaka R, Inayama Y, Takeuchi I. A fatal case of takotsubo cardiomyopathy secondary to refractory hypoglycemia in severe starvation: an autopsy case report. Cureus 2022:1–8. doi:10.7759/cureus.23287.
[29] Mitchell A, Marquis F. Can takotsubo cardiomyopathy be diagnosed by autopsy? Report of a presumed case presenting as cardiac rupture. BMC Clin Pathol 2017;17:1–5. doi:10.1186/s12907-017-0045-0.
[30] Mizutani K, Shioya A, Hirose Y, Saito R, Yamada S. Serious takotsubo cardiomyopathy: an autopsy case presenting severe irreversible myocardial damage after frequent episodes of recurrence. Diagn Pathol 2020;15. doi:10.1186/s13000-020-01006-x.
[31] Toni C, Iannaccone F, Chella P, Basolo F, Pucci A. Sudden death in a case of recurrent Takotsubo syndrome. Forensic Sci Med Pathol 2019;15:595–7. doi:10.1007/s12024-019-00163-w.
[32] Tran K, Milne N, Duhig E, Altman M. Inverted takotsubo cardiomyopathy - clinicopathologic correlation. Am J Forensic Med Pathol 2013;34:217–21. doi:10.1097/PAF.0b013e31829f653e.
[33] Tsunoda S, Tando S, Doi T, Kitamura Y, Ogawa M, ichi Tanabe S, Oda Y. Left ventricular free wall rupture associated with a combination of acute myocardial infarction and stress-provoked cardiomyopathy: an autopsy case. J Cardiol Cases 2010;2. doi:10.1016/j.jccase.2010.05.006.
[34] Grassi S, Campuzano O, Coll M, Cazzato F, Sarquella-Brugada G, Rossi R, Oliva A. Update on the diagnostic pitfalls of autopsy and post-mortem genetic testing in cardiomyopathies. Int J Mol Sci 2021;22:4124. doi:10.3390/ijms22084124.
[35] Kurisu S, Inoue I. Cardiac rupture in tako-tsubo cardiomyopathy with persistent ST-segment elevation. Int J Cardiol 2012;158:e5–6. doi:10.1016/j.ijcard.2011.10.059.
[36] Jaguszewski M, Fijalkowski M, Nowak R, Czapiewski P, Ghadri J-R, Templin C, Rynkiewicz A. Ventricular rupture in Takotsubo cardiomyopathy. Eur Heart J 2012;33 1027–1027. doi:10.1093/eurheartj/ehs054.
[37] Bybee KA, Prasad A. Stress-Related Cardiomyopathy Syndromes. Circulation 2008;118:397–409. doi:10.1161/CIRCULATIONAHA.106.677625.
[38] Maréchaux S, Fornes P, Petit S, Poisson C, Thevenin D, Tourneau TLe, Ennezat P-V. Pathology of inverted Takotsubo cardiomyopathy. Cardiovasc Pathol 2008;17:241–3. doi:10.1016/j.carpath.2007.08.002.
[39] Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy. Circulation 2008;118:2754–62. doi:10.1161/CIRCULATIONAHA.108.767012.
[40] de Gregorio C, Pistelli L, Borgi M, Trio O, Akashi YJ, Andò G. TakoTsubo syndrome: a well-known disease but not everything is clear yet. Rev Cardiovasc Med 2022;23:184. doi:10.31083/j.rcm2306184.
[41] Ferradini V, Vacca D, Belmonte B, Mango R, Scola L, Novelli G, Sangiuolo F. Genetic and epigenetic factors of Takotsubo syndrome: a systematic review. Int J Mol Sci 2021;22:9875. doi:10.3390/ijms22189875.
[42] Grassi S, Campuzano O, Coll M, Cazzato F, Iglesias A, Ausania F, Brugada R. Eosinophilic infiltration of the sino-atrial node in sudden cardiac death caused by long QT syndrome. Int J Mol Sci 2022;23:11666. doi:10.3390/ijms231911666.