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Editorial board member of *World Journal of Cardiology*, Professor Mohamed Bamoshmoosh completed his MD and specialization in cardiology at Florence University (Italy), and worked for ten years at the Italian National Research Council. His ongoing research interests involve evaluation of cardiovascular risk factors and cardiovascular diseases in the developing countries and in ethnic minorities in Europe. He is responsible for the Advanced Cardiac Imaging Unit at Fanfani Clinical Research Institute in Florence. He also serves as Professor at the University of Science and Technology of Sana'a (Yemen) and a visiting Professor at Aden University (Yemen) and collaborates with Florence University. He is a Distinguished Fellow of the Italian Society of Cardiology (ANMCO). (L-Editor: Filipodia)

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MINIREVIEWS

Frailty, sarcopenia and cachexia in heart failure patients: Different clinical entities of the same painting

Matteo Beltrami, Carlo Fumagalli, Massimo Milli

ORCID number: Matteo Beltrami 0000-0001-7161-3224; Carlo Fumagalli 0000-0001-7963-5049; Massimo Milli 0000-0003-4811-6224.

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Matteo Beltrami, Massimo Milli, Cardiology Unit, San Giovanni di Dio Hospital, Florence 50142, Italy

Carlo Fumagalli, Cardiomyopathy Unit, Careggi University Hospital, Florence 50139, Italy

Corresponding author: Matteo Beltrami, MD, Doctor, Postdoc, Cardiology Unit, San Giovanni di Dio Hospital, 3 Via Torregalli, Florence 50142, Italy. beltrami.matteo1@gmail.com

Abstract

Heart Failure (HF) in elderly patients is a systemic syndrome where advanced age, comorbidities with organ system deterioration, frailty and impaired cognition significantly impact outcome. Cardiac cachexia, sarcopenia and frailty despite overlap in definitions are different clinical entities that frequently coexist in HF patients. However, these co-factors often remain unaddressed, resulting in poor quality-of-life, prolonged physical disability and exercise intolerance and finally with higher rehospitalization rates and mortality. Strategy aim to increase muscle mass and muscle strength and delay the occurrence of frailty state appear essential in this regard. Common HF drugs therapy (b-blockers, angiotensin-converting enzyme inhibitors) and prescription of physical exercise program remain the cornerstone of therapeutic approach in HF patients with new promising data regarding nutritional supplementation. However, the treatment of all these conditions still remain debated and only a profound knowledge of the specific mechanisms and patterns of disease progression will allow to use the appropriate therapy in a given clinical setting. For all these reasons we briefly review current knowledge on frailty, sarcopenia and cachexia in HF patients with the attempt to define clinically significant degrees of multiorgan dysfunction, specific "red alert" thresholds in clinical practice and therapeutic approach.

Key Words: Heart failure; Sarcopenia; Cachexia; Frailty; Terapheutic implication; Comorbidities

Core Tip: The last heart failure (HF) guidelines of the European Society of Cardiology dedicate a chapter each for cachexia, sarcopenia and frailty and several studies

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regarding these topics are coming up. This wealth of information highlights the importance of these co-factors in HF management and are each uniquely relevant to evaluate older patients with HF. It is time to routinely assess cachexia, sarcopenia and frailty that could help in personalized care plan, improve outcomes and reduce hospitalization and institutionalization. However, definitions, pathophysiology and treatment of all these conditions still remain unclear and we briefly summarize the most recent knowledge available in literature.

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INTRODUCTION

Heart failure (HF) in elderly patients is a systemic syndrome where advanced age, comorbidities with organ system deterioration, frailty and impaired cognition significantly impact outcome[1]. HF syndrome shows a significant impact on the health-care resources and its occurrence is ever increasing in the elderly[2]. Recently there are discussion regarding frailty and the common problems affecting skeletal muscle, both sarcopenia and cachexia. These comorbidities are crucial issue to plan health care resources for older patient with HF. After hospitalization for acute HF, these co-factors often remain unaddressed resulting in prolonged physical disability, poor quality-of-life, exercise intolerance and finally with higher rehospitalization rates and mortality. Besides, HF hospitalization independently and significantly increased the risk of limitations of Basic and Instrumental Activities of Daily Living (IADL)[3]. The complex relationship between frailty, muscle wasting and cachexia can coexist and different strategies and interventions need to be deeply investigated to improve outcome, quality of life and HF-related re-admissions. For all these reasons we briefly review current knowledge on frailty, sarcopenia and cachexia in HF patients with the attempt to define clinically significant degrees of multiorgan dysfunction, specific "red alert" thresholds in clinical practice and therapeutic approach.

FRAILTY IN HF

Frailty recognize a biologic basis and it is characterized by a loss of strength and physical ability with a progressive decline of cognitive function. Incorrect definition includes this syndrome as a comorbidity or a disability, but comorbidity is a risk factor and disability is an outcome of frailty state[4]. Frailty patients show a strong susceptibility to several endogenous and exogenous stressors. This vulnerability state contributes to risk of falls, hospitalization and death. Frailty is a common finding in HF patients and the prevalence is higher in older age and correlates significantly with HF severity, however frailty must not be considered only in older individuals and all patients with HF deserve a frailty assessment[5]. FRAIL-HF study reveal the presence of frailty state in 70% of patients with HF and ≥ 80 years old. On the other hand frail patients show an higher risk to develop HF[6]. Several frailty score and pre-fail status assessment are now available; Clinical Frailty Scale, gait speed test, PRISMA/7 questionnaire, Fried Score, FRAIL Score and Short Physical Performance Battery (SPPB) are routinely used in clinical practice with good agreement between methods[7-9]. Recently the HF Association/European Society of Cardiology establish a new frailty score that is the first elaborated in HF setting. This new score consider a 4-domain framework such as clinical, functional, cognitive-psychological and social variables, extremely useful and practical to diagnose frailty in HF patients[10] (Table 1). Nowadays an overall geriatric assessment that consider not only the frailty state but also depression, cognitive impairment and muscle wasting are each uniquely relevant to evaluate older patients with HF and significantly impact prognosis and treatment success (*i.e.*, transcatheter or surgical Aortic Valve Replacement)[11,12]. The SPPB is a set of objective measures of physical performance, highly predictive of disability, hospitalization, institutionalization, and mortality in community-dwelling older

Table 1 Current definitions of frailty, cachexia and sarcopenia

Institution/authors, journal, year	Frailty	Institution/authors, journal, year	Cachexia	Institution/authors, journal, year	Sarcopenia
British Geriatrics Society, Age UK and Royal College of General Practitioners Report[7]. *Age Aging* 2014	(1) A gait speed < 0.8 m/s; (2) Timed-up-and-go test > 10 s; (3) Score of ≥ 3 on the PRISMA 7 questionnaire. Falls, delirium and sudden immobility can used to indicate the presence of frailty	Argilés *et al*[19]. Consensus on cachexia definitions. *J Am Med Dir Assoc* 2010	Weight loss > 5% of body weight (or BMI < 20 kg/m^2) in ≤ 1 year in presence of chronic illness and three of five of these criteria. (1) Decreased muscle strength; (2) Fatigue; (3) Anorexia; (4) Low fat free mass index; (5) Anaemia (< 120 g/L), low serum albumin (< 32 g/L) and CRP > 5 mg/L, IL-6 > 4 pg/mL	Revised European consensus on definition and diagnosis[36]. *Age Aging* 2019	(1) Low muscle strength; (2) Evidence of low muscle quantity or quality; (3) Detection of low physical performance. The combination of three represent severe sarcopenia
Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure[10]. *Eur J Heart Fail* 2019	The frailty score in HF patients were built with the following variables: (1) Clinical: Comorbidities, weight loss, falls; (2) Psycho-cognitive: Cognitive impairment, dementia, depression; (3) Functional: ADL/IADL, mobility, balance; (4) Social: Living alone, no social support, institutionalisation	International Consensus on Cancer Cachexia Classification[65]. *Lancet* 2003	The agreed diagnostic criterion for cachexia was weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (BMI < 20 kg/m^2) or skeletal muscle mass reduction	Society of Sarcopenia, Cachexia and Wasting Disorders[37]. *J Am Med Dir Assoc* 2011	Muscle loss with (1) walking speed equal or less than 1 m/s; (2) walks less than 400 m during a 6-minute walk. Appendicular lean mass/height2 > 2 SD below the mean mass of a healthy person (aged 20–30 yr)
Fried *et al*[4]. *J Gerontol A Biol Sci Med Sci* 2001	Frailty was defined with three or more of the following criteria: (1) Unintentional weight loss (4, 5 kgs in past year); (2) Self-reported exhaustion; (3) Weakness (reduced grip strength); (4) Slow walking speed; (5) Low physical activity. A pre-frail status is accordingly whit one or two criteria	SCRINIO working group[66]. *JPEN J Parenter Enteral Nutr* 2009	The patients were divided in 4 groups based on combinations of body weight loss < 10% in precachexia and ≥ 10% in cachexia; associated to the presence/absence of at least 1 symptom of anorexia, fatigue or early satiation	International working group on sarcopenia[39]. *J Am Med Dir Assoc* 2011	Gait speed of less than 1 ms (-1) and low muscle mass (appendicular mass relative to ht (2) that is ≤ 7.23 kg/m^2 in men and ≤ 5.67 kg/m^2 in women)
Canadian Study of Health and Aging[9]. *CMAJ* 2005	Clinical frailty scale is based on IADL, activity, mobility, energy, and symptoms all associated with clinical judgement			Special Interest Groups "Cachexia-Anorexia in Chronic wasting diseases" and "Nutrition in Geriatrics"[21]. *Clin Nutr* 2008	Reduced muscle mass, strength and function (low handgrip strength (men < 26 kg, women < 16 kg), gait speed ≤ 0.8 m/s, low appendicular lean mass/BMI)

BMI: Body mass index; IL-6: Interleukin-6; hg: Height; kgs: Kilograms; CRP: C-reactive protein; IADL: Instrumental activities of daily living.

individuals[13,14]. The prognostic potential of the instrument has been proven in patients hospitalized for HF, pneumonia, chronic obstructive pulmonary disease (COPD) and minor stroke[15]. Furthermore, in a cohort of hospitalized elderly HF patients, a low physical performance status, as evaluated with SPPB, predicted mortality even after adjustment for left ventricle ejection fraction (LVEF), New York Heart Association (NYHA) Class and comorbidities[16]. Moreover, handgrip strength, serum albumin and IADL status are all associated with health outcome in elderly patients hospitalized for HF. Moreover, the pre-frailty state, a condition that is potentially reversible, identified by slow gait speed, exhaustion and low energy expenditure, is in the same way an independent predictor of new cardiovascular events in older adults[17]. For all these reasons closer follow up by HF team is highly necessary in frail patients. This approach could monitor HF symptoms, adjust medications and address reversible causes leading to worsening of frailty score and consequent HF decompensation.

CARDIAC CACHEXIA IN HF

Cachexia is a serious but underrecognized consequence of many chronic diseases such as cancers, COPD, malnutrition state, neurological disease, rheumatoid arthritis and kidney disease. It is considered a wasting process at multiorgan levels (skeletal muscle, fat and bone tissue)[18]. Cachexia is defined by a weight loss > 5% of body weight [or body mass index (BMI) < 20 kg/m^2] in ≤ 1 year in presence of chronic illness and three of five of these criteria (1) decreased muscle strength; (2) fatigue; (3) anorexia; (4) low fat free mass index; and (5) abnormal biochemistry [anaemia (< 120 g/L), low serum albumin (< 32 g/L), increased inflammatory markers (C-reactive protein > 5 mg/L), interleukin-6 (IL-6) > 4 pg/mL][19] (Table 1). The overall prevalence in Western World is still growing and affects around 1% of patients population[20,21]. Cachexia is more frequently common in end-stage HF, its prevalence ranges from 5%-15%[22], but surprisingly it is not clear a close relationship with LVEF, in particular the prevalence of the disease is the same in various HF phenotype[23]. In a prospective study that enrolled outpatients with LVEF ≤ 40%, 18% are cachectic and cardiac cachexia is associated with intestinal congestion irrespective of HF stage and cardiac function. Inflammation state, gastrointestinal discomfort, appetite loss provide probable mechanisms, by which intestinal congestion may trigger cardiac cachexia[24]. Instead right ventricular dysfunction and weight loss may have a pathophysiological linked (venous congestion, malabsorption, anorexia, gut bacteria translocation)[25]; improvement of right ventricular function may delay the occurrence of cachexia. Moreover, tricuspid regurgitation and pulmonary hypertension are associated with low BMI and they are accentuating risk factor for cachexia, together with hypoalbuminemia and hyponatremia due to protein-losing enteropathy[26,27].

Cachectic patients show an impaired functional capacity, more severe symptoms and low quality of life[28]. This serious complication is associated with frequent hospitalization increased length of in hospital stay and health care cost[29]. Weight loss displays an additional prognostic information beyond clinical features of HF severity with significant association with morbidity and mortality[30]. Wasting disorders is and independent risk factor for impaired survival in chronic HF patients (adjusting for age, sex, NYHA class, LVEF, and VO2 consumption); mortality at 18 months of followup is around 50% in patients with cachexia[31]. In hospitalized HF patients with cardiac cachexia factors such renal function, age, and haemoglobin are pivotal prognostic markers[32].

As opposite, obesity is an independent risk factor associated with HF, but recently it is well demonstrated that obesity in patients that have already developed HF (across a wide range of BMI) is related to lower mortality; highlighting the concept of "obesity paradox" also common in other chronic disease[33]. However, BMI does not reflect the body composition regarding the percentage of fat mass, fat-free mass and lean mass. Inside this different large spectrum of body composition, patients with preserved skeletal muscle mass show a better prognosis compared with patients with reduced lean mass due to increased stroke volume and consequent better tissue perfusion[34]. Thus, fat mass loss but not lean mass has a prognostic impact and it is a good indicator of enhanced catabolism and has a role of cardioprotection in advanced HF.

SARCOPENIA IN HF

Recently the 12th Cachexia Conference held in Berlin in December 2019 highlights preclinical and clinical studies in the field of wasting disorders[35]. The definition of sarcopenia remains a matter of discussion, however for the first time it is recognized that strength is better than mass to evaluate adverse outcomes and actually the European consensus on definition and diagnosis Sarcopenia define the disease with three criterion: (1) Low muscle strength, that is considered the most accurate parameter to evaluate sarcopenia; (2) Evidence of low muscle quantity or quality; and (3) The detection of low physical performance (Table 1). The presence of all three criteria permit to define ad advance sarcopenia status. Several tests and different tools are widely described to assess sarcopenia in practice and in research with specific description of each method used[36-39]. Sarcopenia is age related and old muscle mass is reduced by 1%-2% annually after 50 years old with a contemporary decline in muscle strength by about 1.5%[40]. Its prevalence increases around 3% annually after the 60 years old[41]. For the first time the European Society of Cardiology in the guidelines of 2016 dedicate a chapter to cachexia and sarcopenia recognizing as important comorbidities of HF[42]. The prevalence of sarcopenia is around 20% in HF with

reduced ejection fraction (HFrEF) and HF with preserved ejection fraction patients without clear difference in prevalence across different HF phenotype. A monotonic association existed between increasing sarcopenia prevalence and other comorbidities, in particular sarcopenia correlates with the decline of glomerular filtration rate[43,44]. Six-minutes-walk test and spiroergometry show lower Vitamin E/VCO2 (VO2) and shorter exercise time in sarcopenic HF patients, highlighting the impact of muscle wasting in lower muscle strength and lower physical performance in HF population. Bekfani *et al*[45] find better quality of life in patients with higher values of muscle strength/muscle mass ratio (evaluated by Visual Analogue Scale derived from the EQ-5D)[45]. Emami *et al*[46] demonstrate a percentage of overlap (6.7% in HF population studied) of both sarcopenia and cachexia. The lowest values of muscle strength and function, as assessed by handgrip and quadriceps strength, 6 min walking test, SPPB score and peak VO2, are observed only in sarcopenic groups[46]. Moreover, sarcopenia significantly impact the functional capacity of HF patients; and it is associated with increased likelihood of adverse events including falls, fractures, worst neurocognitive profile and low physical performance that may precipitate a relative clinical HF stable condition. In older patients low physical activity is strictly related with the occurrence of sarcopenia and it is an independent factor in prolonging hospital stay among patients admitted to hospital care[47]. However, muscle wasting might be present also in younger patients with HF and non-ischemic dilated cardiomyopathy, particularly in those with advance clinical status[48]. In literature, some discordant opinions are evident regarding the recovery of skeletal muscle after heart transplantation (HT) or left ventricle assistant device implantation[49]. Skeletal muscle impairment seems to persist after months from HT and contribute to the impaired exercise capacity[50], however a recent study demonstrates the recovery of muscle mass and strength after 1.5-3 years of follow up after HT. Moreover, HT and ventricular assist device therapy lead to an improvement in frailty score during follow up highlighting that sarcopenia and frailty are both dynamic and not a fixed entity[51].

BASIC PATHOPHYSIOLOGICAL OVERVIEW

Cardiac cachexia, sarcopenia and frailty in HF patients recognize similar pathophysiological features (Figure 1). Systemic inflammation and hypermetabolism play a pivotal role; cachectic patients display an increased cortisol/dehydroepiandrosterone ratio and higher cytokine levels such as tumor necrosis factor (TNF)-alpha, soluble TNF-receptor 1 and IL-6. Higher levels of hormones and cytokines activities are both associated with muscle wasting, reduced fat tissue and bone mass. Few hormones are implicated in the pathophysiology in cachexia and sarcopenia. Growth hormone, insulin resistance and insulin-like growth factor-1 levels are all associated with muscle mass loss and consequently with a significant reduction of physical performance[52]. Triiodothyronine in cachectic oncologic patients is increased compared to non-cachectic cancer patients and it is also normal in patients with benign weight loss. Ghrelin significantly inhibits the production of cytokines with inflammatory pathway and exhibits anti-cachectic activity both with growth hormone dependent and independent mechanisms. Low testosterone levels are usually common in all HF patients and contribute to the progression of cardiac cachexia, sarcopenia and frailty through altered peripheral vascular resistance, increased cardiac afterload, and decreased cardiac output. Nutritional alterations and gastrointestinal malabsorption lead to an abnormal calorie uptake, protein balance and insulin resistance[53]. Advanced HF status is linked to gastroenteropathy secondary to intestinal edema that result in protein losing enteropathy which causes malabsorption and anorexia[54]. Catabolic/anabolic imbalance change the substrate utilization in tissues. Moreover, cachexia in HF is associated with an increase in adiponectin concentration strictly related to type B natriuretic peptide levels[55]. All these reasons exacerbate the wasting process and muscle cells apoptosis, and therefore result in muscle atrophy and lower muscular strength favoring the occurrence of frailty[56].

TERAPHEUTIC IMPLICATION

Physical inactivity due to the progression of HF syndrome are common in frailty patients. Sarcopenic, cachectic and frailty patients show impaired exercise capacity and limitations in common activity such as food preparation and eating, contributing to disability and muscle loss. Skeletal muscle improvement after exercise training

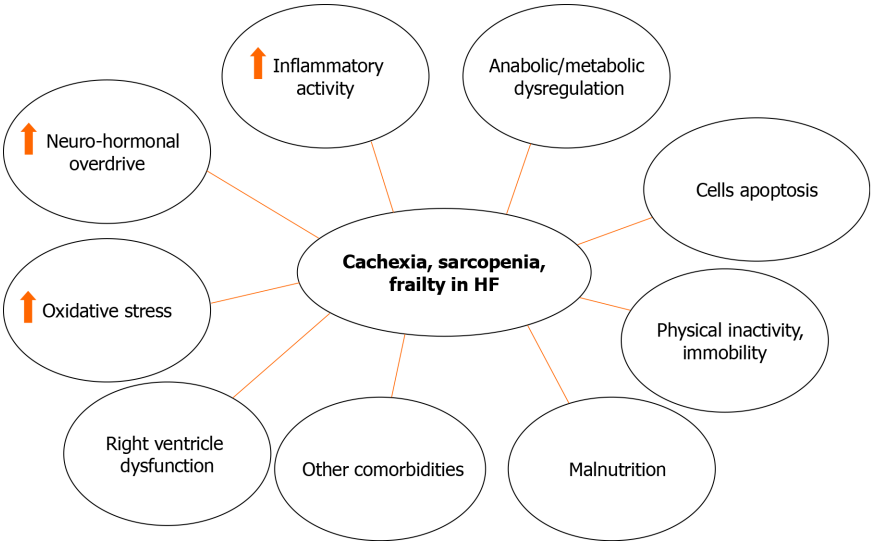

Figure 1 Pathophysiological mechanism and contributing factors leading to cachexia, sarcopenia and frailty in heart failure. HF: Heart failure.

explain the reduction of maximal oxygen consumption demonstrating how physical activity is the major treatment of these patients[57]. Physical exercise program and nutritional supplementation are more effective in individuals with low functional level and increased number of frailty criteria[58]. Growing evidence show a potential benefit from oral supplementation in terms of protein and energy intake in HF patients with the aim to avoid the loss of lean mass[59,60], this personalized dietary intervention results in a potential benefit with significant impact in reducing mortality and hospital readmission. In sarcopenic patients potential treatments may include appetite stimulants and anabolic agents, including testosterone, in combination with the application of nutritional supplements and anti-catabolic interventions, although none is of proven benefit and their safety is unknown[61]. However, scientific data are scarce and the quality of the evidence is low, and no strong recommendations can be currently made in HF setting[62].

In patients with HFrEF and sinus rhythm, b-blockers significantly improve the outcome due its effect on weight gain counterpoising the sympathetic activation that it is an important determinant of cardiac cachexia[63]. Moreover treatment with an angiotensin-converting enzyme (ACE) inhibitor (enalapril) reduces the risk of weight loss in patients with HFrEF[64-66].

CONCLUSION

Cardiac cachexia, sarcopenia and frailty despite overlap in definitions are different clinical entities that frequently coexist in HF patients. All these conditions are serious complications in HF patients and are associated with increasing hospitalization and mortality rates[1]. It is time to produce an important effort to include a routinely assessment in clinical practice of cachexia, sarcopenia and frailty for HF patients that could help in earlier therapeutic decision, personalized care plan, improve outcomes and reduce hospitalization and institutionalization. Strategy aim to increase muscle mass and muscle strength and delay the occurrence of frailty state appear essential in this regard. Common HF drugs therapy (b-blockers, ACE inhibitors) and prescription of physical exercise program remain the cornerstone of therapeutic approach in HF patients with new promising data regarding nutritional supplementation. However, the treatment of all these conditions still remain debated and only a profound knowledge of the specific mechanisms and patterns of disease progression will allow to use the appropriate therapy in a given clinical setting.

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ORIGINAL ARTICLE

Retrospective Study

Clinical outcomes in patients with native valve infective endocarditis and diabetes mellitus

Temidayo Abe, Harry Onoriode Eyituoyo, Gabrielle De Allie, Titilope Olanipekun, Valery Sammah Effoe, Kikelomo Olaosebikan, Paul Mather

ORCID number: Temidayo Abe 0000-0001-8371-2000; Harry Onoriode Eyituoyo 0000-0001-6132-6926; Gabrielle De Allie 0000-0002-4855-8789; Titilope Olanipekun 0000-0002-8472-6970; Valery Sammah Effoe 0000-0002-7297-1151; Kikelomo Olaosebikan 0000-0003-2716-5924; Paul Mather 0000-0001-5483-8472.

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Temidayo Abe, Gabrielle De Allie, Titilope Olanipekun, Department of Internal Medicine, Morehouse School of Medicine, Atlanta, GA 30310, United States

Harry Onoriode Eyituoyo, Department of Internal Medicine, Mercer University School of Medicine, Macon, GA 31207, United States

Valery Sammah Effoe, Department of Cardiovascular Disease, Morehouse School of Medicine, Atlanta, GA 30310, United States

Kikelomo Olaosebikan, Department of Medicine, University of Debrecen Medical and Health Science Center, Debrecen 4032, Hungary

Paul Mather, Department of Cardiovascular Disease, University of Pennsylvania, Pennsylvania, PA 19104, United States

Corresponding author: Temidayo Abe, MD, Staff Physician, Department of Internal Medicine, Morehouse School of Medicine, 720 Westview Dr SW, Atlanta, GA 30310, United States. tabe@msm.edu

Abstract

BACKGROUND

There is a lack of data on the clinical outcomes in patients with native valve infective endocarditis (NVIE) and diabetes mellitus (DM).

AIM

To investigate (1) trends in the prevalence of DM among patients with NVIE; and (2) the impact of DM on NVIE outcomes.

METHODS

We identified 76385 with NVIE from the 2004 to 2014 National Inpatient Sample, of which 22284 (28%) had DM. We assessed trends in DM from 2004 to 2014 using the Cochrane Armitage test. We compared baseline comorbidities, microorganisms, and in-patients procedures between those with *vs* without DM. Propensity match analysis and multivariate logistic regression were used to investigate study outcomes in in-hospital mortality, stroke, acute heart failure, cardiogenic shock, septic shock, and atrioventricular block.

RESULTS

database in the United States. Informed patient consent is not required.

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Crude rates of DM increased from in 22% in 2004 to 30% in 2014. There were significant differences in demographics, comorbidities and NVIE risk factors between the two groups. Staphylococcus aureus was the most common organism identified with higher rates in patients with DM (33.1% *vs* 35.6%; $P < 0.0001$). After propensity matching, in-hospital mortality (11.1% *vs* 11.9%; $P < 0.0001$), stroke (2.3% *vs* 3.0%; $P < 0.0001$), acute heart failure (4.6% *vs* 6.5%; $P = 0.001$), cardiogenic shock (1.5% *vs* 1.9%; $P < 0.0001$), septic shock (7.2% *vs* 9.6%; $P < 0.0001$), and atrioventricular block (1.5% *vs* 2.4%; $P < 0.0001$), were significantly higher in patients with DM. Independent predictors of mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age.

CONCLUSION

There is an increasing prevalence of DM in NVIE and it is associated with poorer outcomes. Further studies are crucial to identify the clinical, and sociodemographic contributors to this trend and develop strategies to mitigate its attendant risk.

Key Words: Infective endocarditis; Native valve infective endocarditis; Diabetes mellitus; Valvular heart disease; Cardiovascular disease; National Inpatient Sample

Core Tip: In this observational study, we found increasing prevalence rates for diabetes mellitus (DM) among patients with native valve infective endocarditis (NVIE) from 2004–2014. There were significant differences in risk factors, microbiology, and in-patient procedures between patients with DM compared to those without DM. DM was associated with mortality, acute heart failure, stroke, atrioventricular block, septic shock, and cardiogenic shock. Independent predictors of in-hospital mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age.

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INTRODUCTION

Despite advancements in management strategies, infective endocarditis (IE) is associated with high mortality rates ranging from 10%-26% and an estimated five-year survival rate of 60%-70%[1-4]. Also, IE carries a significant long term morbidity risk with high rates of stroke (24%), and heart failure (49%)[1-4]. One of the challenges associated with IE management is identifying patients at increased risk of complications. While current guidelines recommend active surveillance, early stratification can help identify patients who may benefit from further intervention.

We have seen an increase in hospitalization from native valve infective endocarditis (NVIE) in the United States [from 155151 (2002-2006) to 195300 (2012-2016)][5]. This is likely related to increased risk factors such as drug abuse, advanced age, and diabetes mellitus (DM)[5-9]. There is a paucity of data on the outcomes of NVIE in DM patients. Previous studies looking at DM and IE have been limited by single-center experiences, sample size and analyses that combine NVIE and prosthetic valve infective endocarditis (PVIE)[9-16]. In this study, using a well-characterized database, we investigated trends in the prevalence of DM among patients with NVIE; and the impact of DM on in-hospital mortality, acute heart failure, stroke, septic shock, cardiogenic shock, and atrioventricular block.

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MATERIALS AND METHODS

Study design

Our data source was the National In-patient Sample (NIS) 2004–2014, a subset of the Healthcare Cost Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ)[17,18]. Briefly, NIS and HCUP are the largest all-payer inpatient database in the United States. The database contains a 20% stratified sample of all discharges from United States hospitals representing the United States population and accounts for 90% of all hospitalizations[18]. It includes information on demographics, hospital characteristics, up to 25 diagnostic and procedure codes based on the International Classification of Diseases 9th revision, Clinical Modification (ICD-9-CM), and outcomes based on patient discharge records.

Study population, variables and outcomes

We queried NIS 2004–2014 using ICD-9-CM codes to identify patients age 18 and above, who were hospitalized with the primary diagnosis of acute or subacute IE. To limit the sample to NVIE, we excluded patients with a prior history of valve replacement and cardiac devices (Figure 1). The algorithm has been validated[5]. The cohort was then divided into those with and without DM. Demographics associated with each diagnosis were identified from NIS, and associated comorbidities were extracted from AHRQ[17,18]. This allows the identification of comorbidities that were present before admission. Other variables that could impact study outcomes, such as the type of organism and inpatient procedures, were included in the analysis. The primary endpoint was to investigate the impact of DM on in-hospital mortality, stroke, acute heart failure, cardiogenic shock, septic shock and atrioventricular block in those with NVIE. All clinical characteristics were defined using ICD-9-CM codes (Supplementary Table 1).

Statistical analysis

IBM SPSS V.25 was used for statistical analysis. Statistical significance was defined as $P < 0.05$. We compared baseline characteristics, organisms involved, and inpatient procedures between patients with DM compared to those without DM. Chi-square was used for categorical variables, while an independent student *t*-test was used for continuous variables. We performed trend analysis using the Cochrane-Armitage test to evaluate the temporal trends in the prevalence of DM in patients with NVIE.

We compared the incidence of in-hospital mortality, stroke, acute heart failure, cardiogenic shock, septic shock, and atrioventricular block. Descriptive statistics were reported in frequencies with percentages for categorical variables, while continuous variables were reported in mean, standard deviation, median, and 25th and 75th percentiles. To limit selection bias, we employed propensity score methodology to match hospitalizations with NVIE patients who had DM *vs* those without any DM at a 1:1 ratio. The nearest neighbor technique was adopted to match each case to control, which is closest to the calculated propensity score, with a caliper width of 0.1. The propensity score was calculated from the following 26 matching variables: Age, sex, race, atrial fibrillation, tobacco use disorder, valvular heart disease, hypothyroidism, chronic kidney disease, obesity, hypertension, congestive heart failure, chronic lung disease, hyperlipidemia, hemodialysis, chronic liver disease, peripheral artery disease, coronary artery disease, drug abuse, pulmonary hypertension, human immunodeficiency virus, congenital heart disease, history of cardiac transplant, rheumatic heart disease, staphylococcus aureus, other staphylococcus, viridians, streptococci, enterococci, group A streptococci, group B streptococci, group G streptococci, and gram-negative bacteremia. Multivariate logistic regression was then used to estimate the adjusted odds ratio of the study outcome in those with DM compared to those without DM.

Binomial regression was used to identify variables in the demographics, comorbidities, and microbiology that were associated with mortality. All significant variables were then incorporated into a multivariate logistic regression model to determine the predictors of in-hospital mortality.

RESULTS

We identified 76385 patients with NVIE. Among these patients, 21284 (28%) had DM. The mean age of patients with DM was significantly higher (63.4 ± 14 *vs* 58.2 ± 19; $P < 0.0001$). The most predominant race was White American, and they were less likely to

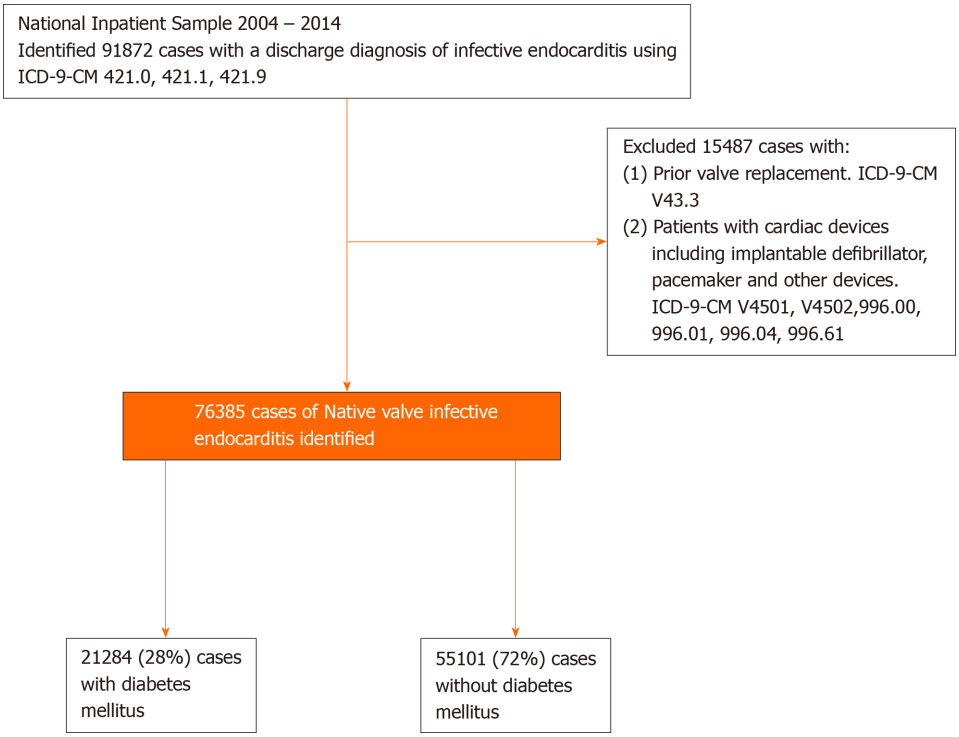


Figure 1 Flow chart of our study design. ICD-9-CM: International Classification of Diseases 9th revision, Clinical Modification.

have DM compared to African, Hispanics, Asians, and Native Americans (Table 1). Patients with DM had higher rates of comorbidities, including hypertension, congestive heart failure, dyslipidemia, obesity, coronary artery disease, and pulmonary hypertension compared to those without DM (Table 1). The crude rates of DM in patients with NVIE significantly increased from 22% in 2004 to 30% in 2014; $P < 0.0001$ (Figure 2).

In terms of the infective organism involved, patients with DM had higher rates of staphylococcus aureus (35.6% *vs* 33.1%; $P < 0.0001$), other staphylococcus organisms (6.7% *vs* 5.4%; $P < 0.0001$), enterococci (7.6% *vs* 6.5%; $P < 0.0001$), group B streptococci (1.6% *vs* 1.3%; $P < 0.0001$), and gram-negative organisms (4.8 *vs* 3.8; $P < 0.0001$) (Table 2). For inpatient procedures, DM patients were less likely to undergo surgical valve replacement (8.2% *vs* 10.6%; $P < 0.0001$) (Table 3).

After propensity matching rates of stroke (2.4% *vs* 1.5%; $P < 0.0001$), acute heart failure (6.5% *vs* 4.6%; $P = 0.001$), atrioventricular block (6.5% *vs* 4.6%; $P < 0.0001$), septic shock (9.6% *vs* 7.2%; $P < 0.0001$), cardiogenic shock (1.9% *vs* 1.5%; $P < 0.0001$), and in-hospital mortality (11.9% *vs* 11.1%; $P < 0.0001$), were significantly higher in patients with DM and NVIE, compared to those with NVIE alone. The multivariate logistic regression followed similar trends (Table 4). Predictors of in-hospital mortality in patients with NVIE and DM included hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age (Table 5).

DISCUSSION

In this observational study, we found increasing prevalence rates for DM among patients with NVIE from 2004–2014. There were significant differences in risk factors, microbiology, and in-patient procedures between patients with DM compared to those without DM. DM was associated with mortality, acute heart failure, stroke, atrioventricular block, septic shock, and cardiogenic shock. Independent predictors of in-hospital mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age. Compared to other studies that have investigated the clinical outcomes of DM in IE patients[9-16]. We had a robust sample size. Also, the analyses in these studies combined NVIE and PVIE. It is essential to stratify because the clinical course, management, and outcomes significantly differ[19-21]. Lastly, we identified the independent predictors of mortality.

The overall prevalence of DM was 28%, and the crude rates of DM significantly

Table 1 Baseline characteristics of primary hospitalizations for native valve infective endocarditis by diabetes mellitus in the United States from 2004–2014

Demographics and Co-morbidities	NVIE		
	No DM (%)	DM (%)	*P* value
Age (yr), mean (SD)	58.2 ± 19	63.37 ± 14	< 0.0001
Gender			< 0.0001
Male	58.4	55.6	
Female	41.6	44.4	
Race			< 0.0001
White	71.9	62.5	
Black	15.9	20.0	
Hispanic	7.1	11.2	
Asian	1.8	2.4	
Native Americans	0.6	1.0	
Other	2.7	2.9	
Co-morbidities			
Tobacco abuse	14.8	9.0	< 0.0001
Hypothyroidism	6.2	9.6	< 0.0001
Hyperlipidemia	11.5	25.1	< 0.0001
Valvular heart diseases	21.6	19.0	< 0.0001
Chronic kidney disease	3.8	7.9	< 0.0001
Obesity	1.8	7.2	< 0.0001
Congestive heart failure	26.2	34.2	< 0.0001
Chronic liver disease	9.3	12.4	< 0.0001
Hypertension	39.1	64.8	< 0.0001
HIV	2.6	0.9	< 0.0001
Atrial fibrillation	18.9	22.4	< 0.0001
Pulmonary hypertension	5.8	6.5	< 0.0001
Coronary artery disease	14.2	29.7	< 0.0001
Peripheral artery disease	2.4	5.5	< 0.0001
Hemodialysis	15.0	27.8	< 0.0001
History of cardiac arrest	0.0	0.1	0.011
History of drug abuse	11.9	3.8	< 0.0001
Congenital heart disease	1.8	0.8	< 0.0001
Rheumatic heart disease	11.8	9.6	< 0.0001

DM: Diabetes mellitus; HIV: Human immunodeficiency virus; SD: Standard deviation; NVIE: Native valve infective endocarditis.

increased from 2004–2014. It should be mentioned that there has been a parallel increase in the prevalence of DM in the United States, which had been attributed to increased risk factors such as obesity, sedentary lifestyle, enhanced detection, and increased longevity[22,23]. A study demonstrated an increased prevalence from 7.7% in 1999-2000 to 13.3% in 2015-2016 among United States adults[24]. In another study using the national health and nutrition examination survey, the prevalence increased from 9.8% in 1988–1994 to 12.4% in 2011–2012, across all age, sex, and racial groups[25].

The clinical profile of NVIE patients with DM was different compared to those without DM. DM patients had higher rates of comorbidities, and IE risk factors such as

Table 2 Infective organisms identified in primary hospitalizations for native valve infective endocarditis by diabetes mellitus in the United States from 2004–2014

Infective organisms	NVIE		
	No DM (%)	DM (%)	*P* value
Staphylococcus aureus	33.1	35.6	< 0.001
Other staphylococcus	5.4	6.7	< 0.001
Viridans streptococci	18.6	15.5	< 0.001
Enterococci	6.5	7.6	< 0.001
Pneumococcus	0.5	0.4	0.11
Group A streptococci	0.7	0.5	0.003
Group B streptococci	1.3	1.6	< 0.001
Group C streptococci	0.1	0.1	0.44
Group G streptococci	0.2	0.2	0.87
Gram negative	3.8	4.8	< 0.001
Anaerobes	0.4	0.3	0.82
Fungemia	0.2	0.2	0.81

DM: Diabetes mellitus; NVIE: Native valve infective endocarditis.

Table 3 Inpatient procedures in primary hospitalizations for native valve infective endocarditis by diabetes mellitus in the United States from 2004–2014

NVIE			
Inpatient procedures	No DM (%)	DM (%)	*P* value
Surgical valve replacement	12.3	9.2	< 0.001
Aortic valve replacement	6.5	5.1	< 0.001
Mitral valve replacement	5.0	3.7	< 0.001
Tricuspid valve replacement	0.1	0.1	0.43
Pulmonary valve replacement	0.7	0.3	< 0.001

Surgical valve replacement, included aortic valve replacement, mitral valve replacement, tricuspid valve replacement and pulmonary valve replacement.
DM: Diabetes mellitus; NVIE: Native valve infective endocarditis.

older age, and hemodialysis. They were less likely to have structural heart disease (valvular heart disease and congenital heart disease) and intravenous drug abuse (Table 1). Several other studies have reported similar findings[8,10,12-14]. We also found significant differences in the organisms involved. DM patients had higher rates of staphylococcus species, enterococci, and gram-negative microorganisms. This is also consistent with prior studies and likely due to increased health care utilization in DM patients, exposing them to nosocomial infections and immune dysfunctions, rendering them more susceptible to skin and soft tissue infections[16,26].

There are a couple of explanations for the poor outcomes among NVIE patients with DM. First, they are more likely to have staphylococcus aureus infections. Staphylococcus aureus tends to stick and multiply on heart valves, promoting vegetation, abscess formation, mechanical complications, and mortality[27-29]. Secondly, IE is characterized by an immunologic response that leads to immune complex formation; the exaggerated immunologic response in DM patients likely contributed to poor outcomes noted in this study[30]. Finally, lower rates of life-saving procedures such a surgical valve replacement, as demonstrated in this study, and higher rates of comorbidities in DM patients are other explanations.

Current IE management strategies center around presumed patient mortality risk. Generally, low-risk patients can be safely managed with antibiotics. At the same time,

Table 4 Association between diabetes mellitus and outcomes of hospitalizations for native valve infective endocarditis after propensity matching

NVIE						
	No DM (%)	DM (%)	aOR	Lower CI	Upper CI	*P* value
In-hospital mortality	11.1	11.9	1.2	1.1	1.4	< 0.0001
Acute heart failure	4.6	6.5	1.2	1.1	1.3	0.001
Stroke	2.3	3.0	1.3	1.1	1.5	< 0.0001
Atrioventricular block	1.5	2.4	1.5	1.3	1.5	< 0.0001
Septic shock	7.2	9.6	1.2	1.1	1.3	< 0.0001
Cardiogenic shock	1.5	1.9	1.4	1.2	1.6	< 0.0001

aOR: Adjusted odds ratio; CI: Confidence interval; DM: Diabetes mellitus; NVIE: Native valve infective endocarditis.

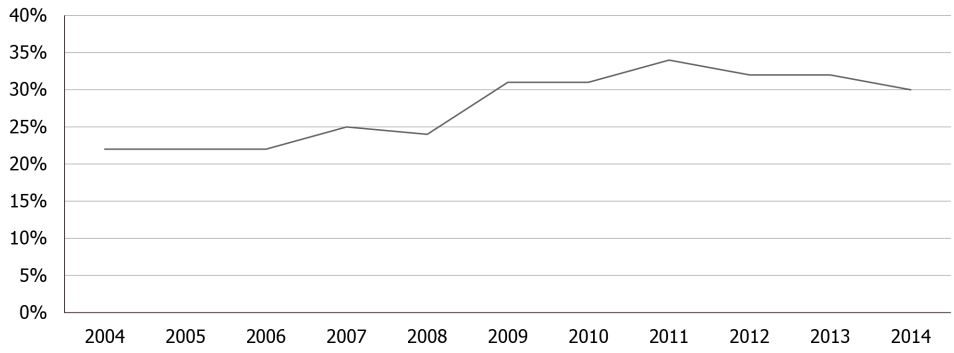
Table 5 Logistic regression analysis for predictors of in hospital mortality among patients with native valve infective endocarditis and diabetes mellitus

	95%CI			
	OR	Lower	Upper	*P* value
Age (yr)				
18-65	REF	REF	REF	REF
> 65	1.02	1.02	1.02	< 0.001
Hypertension	0.56	0.50	0.62	< 0.0001
Atrial fibrillation	1.17	1.05	1.31	0.006
Tobacco abuse	0.74	0.61	0.90	0.003
Hyperlipidemia	0.69	0.61	0.78	< 0.0001
Congestive heart failure	1.34	1.22	1.48	< 0.0001
Chronic liver disease	1.51	1.19	1.92	0.001
Staphylococcus aureus	1.25	1.13	1.39	< 0.0001
Hemodialysis	2.04	1.83	2.27	< 0.0001

CI: Confidence interval; OR: Odds ratio; REF: Reference.

aggressive intervention such as valve replacement is recommended for those at high risk of mortality, suffering from, acute heart failure, large vegetation, and mechanical complications such as valvular dysfunction, and perivalvular abscess[31-34]. These recommendations stem from observational studies demonstrating mortality benefit[31-34]. In this study, odds for in-hospital mortality was 20% higher in DM patients compared to those without DM. Staphylococcus aureus was highly prevalent among patients with DM, and it was significantly associated with mortality. Several other studies have linked staphylococcus aureus to death, likely due to severe valvular damage and complications[4,27,28,34]. Early surgery should be considered in NVIE secondary to staphylococcus aureus, especially in DM patients, due to severe valve destruction and increased mortality.

Other predictors of mortality among DM patients in this study include congestive heart failure, hemodialysis, and atrial fibrillation. This suggests that prevention and aggressive management of comorbid conditions in DM patients could potentially decrease associated NVIE mortality. NVIE is characterized by bacteremia, bacteria colonization, adhesion on cardiac valves and vegetation formation[35]. Immune dysfunction, micro- and macro-angiopathies, and decreased bactericidal activity of the gastrointestinal and genitourinary system make DM patients more susceptible to infections[36]. Tight glycemic control, vaccination, and adequate skin care will help reduce bacteremia and NVIE in DM patients.



Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Diabetes mellitus	22%	22%	22%	25%	24%	31%	31%	34%	32%	32%	30%

Figure 2 Trends in the prevalence of diabetes mellitus among patients with infective endocarditis. $P < 0.0001$.

Some limitations of our study should also be noted. First, data on glycemic control and management of DM were not available. It is well known that strict glycemic control can improve the clinical outcome in patients with DM[4]. Secondly, the study lacked information on clinical variables such as echocardiographic features, vegetation size, and antimicrobials therapy, all of which might impact clinical outcomes[4].

CONCLUSION

Among patients with NVIE, DM is associated with increased mortality and complications. This is likely due to higher rates of staphylococcus bacteremia, underlying comorbidities, and immune dysfunction. Further studies should focus on prevention and management strategies among DM patients with NVIE.

ARTICLE HIGHLIGHTS

Research background

There is a lack of data on the clinical outcomes in patients with native valve infective endocarditis (NVIE) and diabetes mellitus (DM).

Research motivation

Previous studies looking at DM and infective endocarditis (IE) have included analyses that combine NVIE and prosthetic valve IE.

Research objectives

In this study, aim to investigate the temporal trends in the prevalence of DM in NVIE and investigate the impact of DM on NVIE outcomes.

Research methods

The National Inpatient Sample 2004–2014 was queried. Cochrane Armitage test was used for trend analysis. Propensity match scoring and multivariate logistic regression were used to investigate study outcomes (Supplementary Table 2).

Research results

We identified 76385 patients with NVIE, of which 21284 (28%) had DM. Patients with DM had more comorbidities, were more likely to have staphylococcus infection, and less likely to undergo surgical valve replacement. In-hospital mortality, and IE related complications such as stroke, acute heart failure, cardiogenic shock, septic shock, and atrioventricular block, were significantly higher in patients with DM. Independent predictors of mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age.

Research conclusions

There is an increasing prevalence of DM in NVIE and it is associated with poorer outcomes.

Research perspectives

Further studies are crucial to identify the clinical, and sociodemographic contributors to this trend and develop strategies to mitigate its attendant risk.

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CASE REPORT

Myasthenic crisis-induced Takotsubo cardiomyopathy in an elderly man: A case report of an underestimated but deadly combination

Yvonne Kuo, Thomas H Ottens, Ivo van der Bilt, Ruud WM Keunen, Sakir Akin

ORCID number: Yvonne Kuo 0000-0002-2300-0295; Thomas H Ottens 0000-0001-6861-5755; Ivo van der Bilt 0000-0002-1151-2461; Ruud WM Keunen 0000-0001-7186-9641; Sakir Akin 0000-0003-0700-1930.

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Yvonne Kuo, Thomas H Ottens, Sakir Akin, Intensive Care Unit, Hagaziekenhuis, The Hague 2545, Netherlands

Ivo van der Bilt, Department of Cardiology, Hagaziekenhuis, The Hague 2545, Netherlands

Ruud WM Keunen, Department of Neurology, Haga Teaching Hospital, The Hague 2545, Netherlands

Corresponding author: Sakir Akin, MD, PhD, Doctor, Staff Physician, Intensive Care Unit, Hagaziekenhuis, Els Borst-Eilersplein 275 2545 AA The Hague, The Hague 2545, Netherlands. s.akin@hagaziekenhuis.nl

Abstract

BACKGROUND

Patients with myasthenia gravis (MG) are at a higher risk of developing Takotsubo cardiomyopathy (TTC), particularly during a myasthenic crisis. Myasthenic crisis-associated TTC occurs predominantly in women. In this case report, we present a man with metastasized prostate carcinoma who developed TTC after new-onset MG.

CASE SUMMARY

An 81-year-old man with non-insulin dependent diabetes mellitus and metastasized prostate carcinoma presented with dyspnea. During primary assessment examination at the emergency department, there was evident blepharoptosis of his right eye. His electrocardiograms were suggestive of an acute anterior wall myocardial infarction, for which he underwent emergency coronary angiography. No obstructive coronary artery disease was found. During the coronary angiography, the patient developed respiratory failure and was admitted to the Intensive Care Unit for non-invasive respiratory support. The following day, diagnostic neostigmine test revealed a myasthenic crisis. Bedside echocardiography revealed left ventricular apical ballooning with a typical appearance of TTC. Despite the potentially reversible character of both MG and TTC, the patient and family requested an end of support in the Intensive Care Unit due to age and chronic malignancy with reduced quality of life in recent months after non-chemo-responding prostate carcinoma. The patient died soon after treatment withdrawal.

CONCLUSION

Elderly men should be carefully evaluated for TTC when new-onset MG is

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Key Words: Takotsubo cardiomyopathy; Broken heart syndrome; Stress-induced cardiomyopathy; Myasthenic crisis; Respiratory failure; Case report

Core Tip: An elderly man presented with dyspnea and neurological symptoms, including blepharoptosis. Simultaneously, the patient had signs of an acute myocardial infarction, but obstructive coronary artery disease was ruled out by coronary angiogram. Due to respiratory failure, the patient was admitted to the Intensive Care Unit for non-invasive support. The next day, bedside echocardiography revealed left ventricular apical ballooning, typical for Takotsubo cardiomyopathy. Meanwhile, second consultation by the neurologist performing a diagnostic neostigmine test confirmed a myasthenic crisis. Altogether, the patient was diagnosed with a new-onset myasthenic crisis-induced Takotsubo cardiomyopathy. Unfortunately, in this elderly man, this combination was fatal.

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INTRODUCTION

Takotsubo cardiomyopathy (TTC) is a transient cardiac syndrome that typically causes mid-ventricular circumferential and apical hypokinesis mimicking an acute coronary syndrome. In TTC, acute coronary or microvascular spasms can result in stunning of the myocardium with left ventricular dysfunction caused by catecholamine release due to emotion or physical stress[1]. Until 2009, only two cases of patients who had developed TTC after plasmapheresis for a myasthenic crisis were reported[2]. A myasthenic crisis if often the first manifestation of myasthenia gravis (MG). MG is a neuromuscular disease in which autoantibodies are formed against the acetylcholine receptors in the neuromuscular junction, causing severe muscular weakness[2]. The pathophysiology of MG-associated TTC is not exactly clear. A myasthenic crisis can induce severe stress, resulting in excessive catecholamine release. Guaricci *et al*[3] describe a neurogenic/catecholaminergic hypothesis: Supraphysiological levels of epinephrine can paradoxically lead to negative inotropic effects by reducing myofilament contractility, therefore leading to myocardial stunning[3]. Women are 9-times more likely to develop TTC then men. Post-menopausal women are especially prone to TTC[1,4].

Diabetes mellitus is a common comorbidity. When TTC develops during myasthenic crisis, the risk of respiratory failure, intubation and mechanical ventilation (81%) and death (25%) are significant[4,5]. In patients with TTC, respiratory failure is caused by a manifestation of pulmonary edema due to acute heart failure. In MG, however, respiratory distress and failure can be explained by severe skeletal muscle weakness which can lead to hypercapnic failure[6]. However, non-invasive ventilation can successfully stabilize approximately one-third of patients suffering from each of these types of respiratory failure[7,8]. This weakens the awareness that both syndromes can arise during a serious physical and/or emotional stress event. Suspicion of MG with development of pulmonary lung edema should prompt evaluation for TTC. Awareness of the possibility that both MG and TTC may cause respiratory failure, and that an association exists between these conditions, may lead to early recognition, adequate diagnostic work-up and timely treatment.

In this case report, we sought to describe an elderly man with dyspnea who was diagnosed with new-onset MG and TTC.

CASE PRESENTATION

Chief complaints

An 81-year-old man with a medical history of non-insulin dependent diabetes and metastasized prostate carcinoma was referred to our emergency department (ED) by his general practitioner, with complaint of dyspnea and generalized muscle weakness.

History of present illness

The patient had developed walking difficulties, balance impairment and ptosis of his right eye over the past few days, and developed progressive dyspnea in the last few hours before presentation to clinic. The ptosis of the right eye, as well as generalized muscle weakness, were apparent on primary examination in the ED.

History of past illness

The patient was known to have ongoing non-insulin dependent diabetes and metastasized prostate carcinoma.

Physical examination

At the ED, the patient's temperature was 36.5 °C, heart rate was 95 beats per min, respiratory rate 26 was breaths per min, blood pressure was 190/110 mmHg, and oxygen saturation with 3 L O_2 was 96%. The initial neurological examination showed a blepharoptosis, general muscular weakness, and disbalance. As such, our differential diagnosis included peripheral neuromuscular disease related to diabetes mellitus, with considerations for further diagnosis to rule out metastatic disease or paraneoplastic neurological disease. In relation to the patient's complaint of progressive dyspnea, his electrocardiogram (ECG) showed signs of acute coronary syndrome.

Laboratory examinations

Serial ECGs revealed signs of acute anterior wall myocardial infarct, although the patient had no typical symptoms of an acute coronary syndrome (Figure 1). This finding was accompanied by raised serum high-sensitivity troponin levels (maximum 0.814 μg/L; normal range: 0-0.014 μg/L).

Imaging examinations

A conventional X-ray and computed tomography angiography of the chest showed no pulmonary embolism or parenchymal abnormalities, except for atelectasis of both lower lung fields. An emergency coronary angiography showed no obstructive coronary lesions (Figure 2).

Further diagnostic work-up

The patient's respiratory condition quickly deteriorated and he was admitted to the intensive care unit (ICU) with hypercapnic failure, where he was successfully stabilized with non-invasive ventilation (bilevel pressure support). The following day, the typical combination of ptosis and generalized weakness progressing to respiratory failure prompted re-consultation with the neurologist.

MULTIDISCIPLINARY EXPERT CONSULTATION

Ruud Keunen, MD, PhD, Department of Neurology, Haga Teaching Hospital, The Hague, The Netherlands

"The patient should start with mestinon and immunoglobulins treatment if the neostigmine test is positive. Further consideration of steroids has been advised."

Sakir Akin, MD, PhD, Cardiologist-Intensivist, Department of Intensive Care, Haga Teaching Hospital, The Hague, The Netherlands

"The patient should continue inotropic support during continuing acute heart failure. Beside this, there should be ongoing respiratory bilevel non-invasive support to prevent further respiratory complications, accompanied by hypokinetic diaphragm, of myasthenic crisis on top of pulmonary edema by cardiac dysfunction."

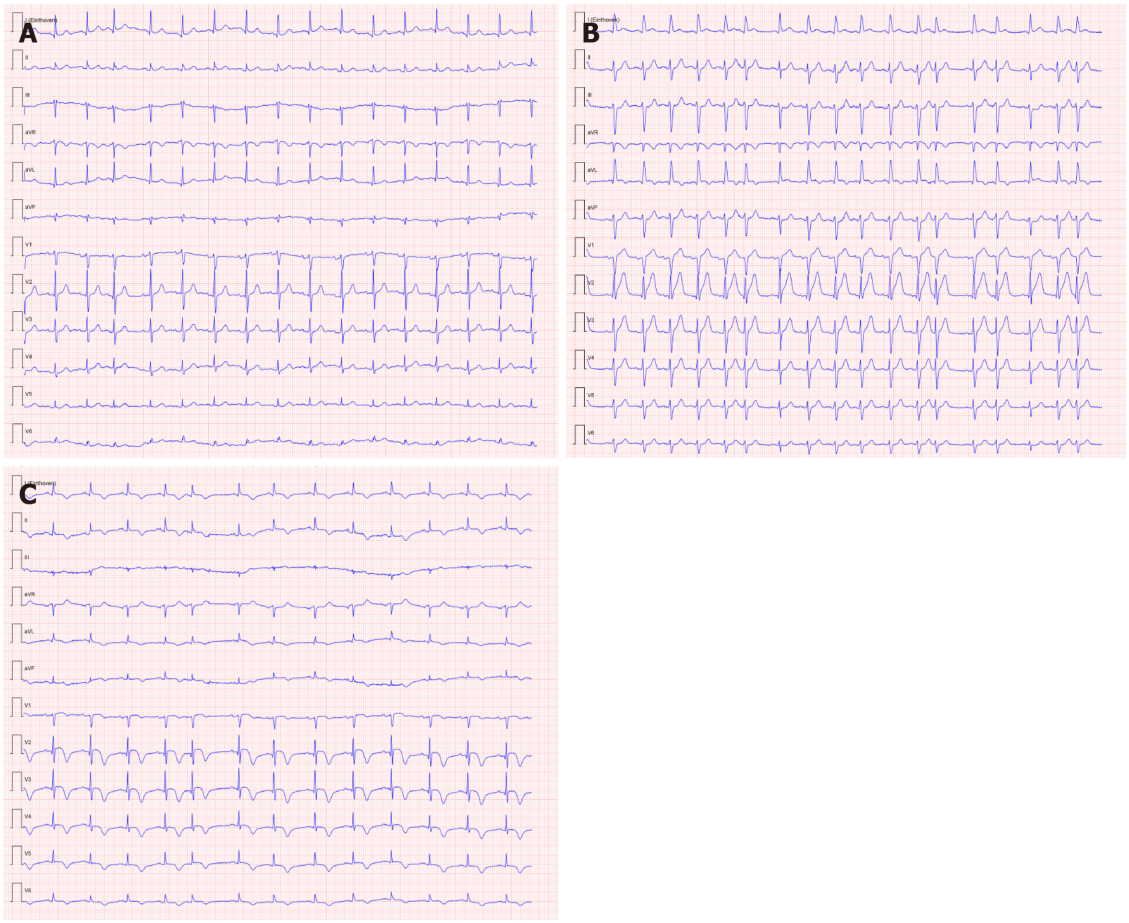

Figure 1 Comparison of electrocardiograms during the myasthenic crisis. A: The electrocardiogram (ECG) was taken upon presentation in the emergency department and showed normal sinus rhythm, with no signs of pathology; B: The second ECG was taken at 4 h after presentation and showed ST-elevation in anterior leads (V1-V4) and lateral leads (I and aVL), with minimal reciprocal depressions in inferior leads (II and aVF) and new T-wave inversion in aVL; C: The third ECG was taken 1 d after presentation to the emergency department and showed evolving ST-elevations in anterior leads, with biphasic T-waves and new inverted T-waves in I, II, aVL and aVF.

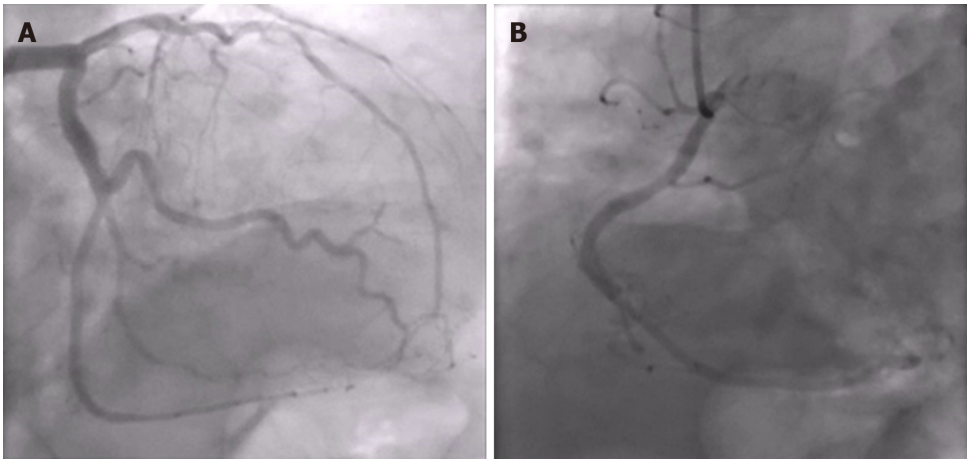

Figure 2 Coronary angiography showed no significant coronary obstruction. A: Left anterior descending artery; B: Right coronary artery.

FINAL DIAGNOSIS

A diagnostic neostigmine test confirmed the diagnosis of myasthenic crisis with new-onset MG. The acetylcholine receptor (known as AChR) antibody was also positive. During his treatment in the ICU, the patient showed signs of progressive hemodynamic instability, requiring inotropic support with dobutamine. Although follow-up ECGs showed a persistent and evolving anterior wall myocardial infarction,

the patient never developed chest pain (Figure 1). Troponin levels also decreased spontaneously. A repeat transthoracic echocardiogram showed apical ballooning of the left ventricle (resembling a Japanese octopus trap) with hypokinesia of the anterior wall, whilst the right ventricle was hyperdynamic but normal in size (Figures 3 and 4). Compared with the quick-look echo carried out in the ED, there was the same morphologic abnormality of the left ventricle. This was suggestive of stress-induced cardiomyopathy, also known as TTC. Theoretically, the myasthenic crisis may have provoked this rare cardiac complication due to excessive catecholamine release. Both MG and TTC are potentially reversible conditions. However, in this specific case of a patient of advanced age and frail physical condition due to chemotherapy-resistant metastasized prostate carcinoma, the clinical condition deteriorated quickly before the effect of intravenous immunoglobulin could occur.

TREATMENT

The patient was supported for neuromuscular failure by non-invasive ventilation and by dobutamin to address the acute heart failure. Despite these treatments, there was ongoing deterioration of his end-organ functions.

OUTCOME AND FOLLOW-UP

On day 3 of ICU treatment, the patient no longer tolerated non-invasive ventilation and became agitated. The patient and his family requested withdrawal of supportive ICU treatment considering the patient's medical history and significantly reduced quality of life in the past few months. After careful evaluation of the patient's wishes, medical history and rapid clinical deterioration, supportive ICU treatments were withdrawn. The patient was given treatment to relieve symptoms and died quickly after withdrawal of supportive therapies.

DISCUSSION

MG is a rare disease in men and even more rarely leads to TTC[4,9]. Symptoms of respiratory failure, blepharoptosis, dysphagia and overall muscle weakness are present in more than half of the patients[5]. In MG patients, women have a higher risk of developing TTC than men, but men have a poorer prognosis. MG-associated TTC may present differently in men and women[1].

In recent years, large cohort studies have attempted to explain the association between MG and TTC. Myasthenic crisis may result in physiologic stress-induced cardiomyopathy, although direct cardiac involvement of MG cannot be ruled out. The golden standard to rule out acute coronary disease is to perform a coronary angiography (CAG). However, this is a relatively invasive and prolonged procedure in which complications can occur, as in our case where the patient became respiratory insufficient during the CAG. An alternative could have been a computed tomography angiography, which is faster and safer as no arterial access is needed, and gives reliable assessment of the coronaries[10]. Although CAG is the golden standard to distinguish acute coronary syndrome from TTC, non-invasive imaging modalities are becoming useful for TTC assessment. Even in emergent situations, echocardiography can provide a good evaluation of TTC. However, poor echo windows could still influence the visibility of ventricular walls. More accurate non-invasive cardiac imaging modalities known from the field of complex congenital anomalies could help to delineate the ventricular walls and refine the diagnosis[11].

MG-associated TTC triggered by a myasthenic crisis is rare. No more than 20 cases are described in depth in the published literature. In a Dutch national representative dataset, we found 175 cases with MC-associated TTC[4,5]. However, the case we present here is unique because of the patient's age, male sex and comorbid malignancy. Triggers of myasthenic crisis and development of TTC seem to be heterogeneous. This rare condition should be suspected even in patients without a prior diagnosis of MG, as is demonstrated in the case we present here.

The number of cases describing the combination of these two diseases are increasing. Although, in many of them, development of TTC is a result of the treatment of MG[12,13]. In our case, there was no relation with the treatment of MG since

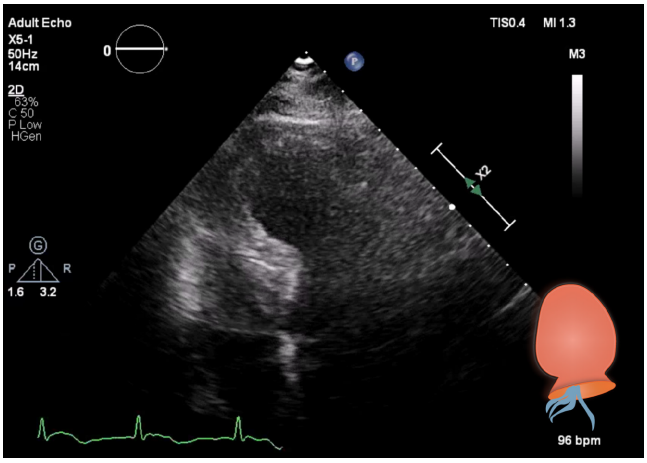

Figure 3 Transthoracic echocardiography in four-chamber view. Apical to mid-ventricular segment ballooning was present at end-systole. Please note the endomyocardial board in end systolic contraction forming apical ballooning of the left ventricle, like a Japanese octopus trap (Takotsubo; see inset illustration), and normal right ventricle size.

Figure 4 Japanese octopus traps, also known as Takotsubo. The shape of Takotsubo resembles apical ballooning.

the patient presented with ventricular dysfunction in the ED where the diagnosis of MG was not yet known. We do not consider it likely that the myasthenic crisis in our patient was related to medication use. The patient had been treated with gosereline injections every 3 mo for an extended period uneventfully.

Based on the literature, our collective experiences and experience with the case that we present as an illustration, we propose that patients with neurological symptoms together with ST-elevation myocardial infarction on the ECG without obstructive coronary lesions should be evaluated with left ventricle angiogram during coronary angiography to exclude TTC. Early initiation of a diagnostic neostigmine test can lead to more awareness of possible new-onset MG in cases of unusual presentation of circulatory instability.

CONCLUSION

We conclude there is a high need for continuous reporting of similar atypical cases to help improve the understanding of this rare entity. Further studies are needed to evaluate possible direct associations between MG and stress-induced TTC.

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CASE REPORT

Anthracycline-induced cardiotoxicity: A case report and review of literature

Esther G Chong, Eric H Lee, Reena Sail, Laura Denham, Gayathri Nagaraj, Chung-Tsen Hsueh

ORCID number: Esther G Chong 0000-0002-0508-9521; Eric H Lee 0000-0002-5273-1652; Reena Sail 0000-0003-0568-4379; Laura Denham 0000-0003-2050-6677; Gayathri Nagaraj 0000-0002-7586-6920; Chung-Tsen Hsueh 0000-0002-1409-0030.

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Esther G Chong, Department of Medicine, Loma Linda University, Loma Linda, CA 92350, United States

Eric H Lee, Department of Hematology/Oncology, Compassionate Cancer Care Medical Group, Fountain Valley, CA 92708, United States

Reena Sail, Department of Hematology/Oncology, Scripps MD Anderson Cancer Center, San Diego, CA 92121, United States

Laura Denham, Department of Pathology and Human Anatomy, Loma Linda University, Loma Linda, CA 92350, United States

Gayathri Nagaraj, Chung-Tsen Hsueh, Division of Medical Oncology and Hematology, Department of Medicine, Loma Linda University, Loma Linda, CA 92350, United States

Corresponding author: Chung-Tsen Hsueh, MD, PhD, Professor, Division of Medical Oncology and Hematology, Department of Medicine, Loma Linda University, 11175 Campus Street, CSP 11015, Loma Linda, CA 92350, United States. chsueh@llu.edu

Abstract

BACKGROUND

Doxorubicin and other anthracycline derivatives inhibit topoisomerase II and is an important class of cytotoxic chemotherapy in cancer treatment. The use of anthracycline is limited by dose-dependent cardiotoxicity, which may manifest initially as asymptomatic cardiac dysfunction with subsequent progression to congestive heart failure. Despite baseline assessment and periodic monitoring of cardiac function for patients receiving anthracycline agents, there are unmet needs in prediction and prevention of anthracycline-induced cardiotoxicity (AIC).

CASE SUMMARY

A 35-year-old African American female was found to have a 9-cm high-grade osteosarcoma of right femur and normal baseline cardiac function with left ventricular ejection fraction of approximately 60%-70% determined by transthoracic and dobutamine stress echocardiogram. She underwent perioperative doxorubicin and cisplatin chemotherapy with 3 cycles before surgery and 3 cycles after surgery, and received a total of 450 mg/m^2 doxorubicin at the end of her treatment course. She was evaluated regularly during chemotherapy without any cardiac or respiratory symptoms. Approximately two months after her last chemotherapy, the patient presented to the emergency

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department with dyspnea for one week and was intubated for acute hypoxic respiratory failure. Echocardiogram showed an ejection fraction of 5%-10% with severe biventricular failure. Despite attempts to optimize cardiac function, the patient's hemodynamic status continued to decline, and resuscitation was not successful on the seventh day of hospitalization. The autopsy showed no evidence of osteosarcoma, and the likely cause of death was cardiac failure with the evidence of pulmonary congestion, liver congestion, and multiple body cavity effusions.

CONCLUSION
We present a case of 35-year-old African American female developing cardiogenic shock shortly after receiving a cumulative dose of 450 mg/m^2 doxorubicin over 9 mo. Cardiac monitoring and management of patients receiving anthracycline chemotherapy have been an area of intense research since introduction of these agents in clinical practice. We have reviewed literature and recent advances in the prediction and prevention of AIC. Although risk factors currently identified can help stratify patients who need closer monitoring, there are limitations to our current understanding and further research is needed in this field.

Key Words: Anthracycline; Cardiotoxicity; Doxorubicin; Troponin; Brain natriuretic peptide; Case report

Core Tip: Anthracyclines may exert a direct toxic effect on cardiac myocytes, precipitating symptomatic heart failure. The case presented demonstrates an example of acute heart failure in a well-compensated young adult who did not at first glance warrant greater than routine cardiac surveillance during doxorubicin treatment course. Utilization of cardioprotective agents and cardiac strain markers such as troponin and brain natriuretic peptide may help to prevent and identify cardiac dysfunction in asymptomatic patients. Prevention of anthracycline-induced cardiotoxicity and cardiovascular toxicities of other anti-cancer therapy requires multidisciplinary approaches such as modification of cardiovascular risk factors, active management of comorbidities, and pharmacologic therapy in selected patients.

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INTRODUCTION

Anthracycline is a class of commonly used agents for the treatment of solid and hematologic cancers. Cardiotoxicity is a well-documented side effect of anthracycline, likely due to free radical damage and DNA strand breakage in cardiomyocytes[1]. Anthracycline-induced cardiotoxicity (AIC) accounts for greater than 30% of cardiotoxicity from cancer-related therapy[2]. When symptoms and signs of cardiotoxicity such as congestive heart failure are identified early, discontinuation of anthracycline, initiating appropriate medical management followed by frequent monitoring of cardiac function can help to alleviate further decline of cardiac function. When a patient is asymptomatic, it is difficult to predict adverse outcomes or plan appropriate frequency of cardiac monitoring.

Here we present a case of an unusual course of AIC in a 35-year-old African American female who received a cumulative dose of 450 mg/m^2 doxorubicin over 9 mo. We also discuss measures and methods that have been reported for early identification and prevention of deterioration of cardiac function.

CASE PRESENTATION

Chief complaints

A 35-year-old African American female without significant past medical history presented to the orthopedic clinic for evaluation of a right knee mass measuring about 5 cm × 9 cm × 6 cm at distal thigh that had been growing in size over the past six months.

History of present illness

A magnetic resonance imaging (MRI) of the knee showed a 5.6 cm × 9.1 cm × 6.0 cm tumor of the distal right femur, and biopsy revealed high-grade osteoblastic osteosarcoma. Further imaging studies including (18)F-fluorodeoxyglucose positron emission tomography/computed tomography (CT) did not indicate distant metastatic disease, and she was referred to medical oncology clinic for pre-operative chemotherapy. At the time of her pre-treatment evaluation, the patient had no chronic medical issues and was not taking any medications. There was no cancer or cardiovascular disease in her family. She had normal complete blood count and comprehensive metabolic panel results. CT scan of chest showed no evidence of pulmonary metastasis, and baseline transthoracic and dobutamine stress echocardiogram showed normal cardiac function with normal right ventricular systolic function and left ventricular ejection fraction (LVEF) 60%-70%.

The patient underwent three cycles of cisplatin and doxorubicin before undergoing resection of the tumor and a total right knee replacement. She had a follow-up echocardiogram after 2 cycles of chemotherapy which again showed normal cardiac function with LVEF 70%. Additionally, she had serial blood tests done for troponin and brain natriuretic peptide (BNP) during hospitalization for neutropenic infection with respiratory symptoms after cycle 2 chemotherapy, and dehydration with hypokalemia after cycle 3 chemotherapy; all the troponin levels were within normal limit except transient increase in BNP with subsequent normalization was noted after cycle 3 chemotherapy. Surgical pathology showed 5% tumor necrosis, and restaging CT and bone scan after surgery showed no evidence of metastatic disease. The patient subsequently completed three more cycles of cisplatin and doxorubicin with good tolerance. While on chemotherapy treatment, she experienced fatigue, nausea, alopecia, and neutropenic infection despite using granulocyte colony stimulating factor, prophylactic antibiotics, and other supportive care measures. She was evaluated every 3-4 wk with history and physical examination, as well as routine laboratory tests.

Approximately two months after her last chemotherapy, she was seen in the medical oncology clinic with an unremarkable history and physical examination. One week later, she presented to the emergency department with complaints of sudden onset of dyspnea, palpitations, and left-sided chest pain. CT angiography of chest showed no pulmonary embolism, but found new right lower lobe indeterminate nodules, measuring up to 7 mm, a small focus of airspace disease in the peripheral right lower lobe, and mild interstitial pulmonary edema. Echocardiogram showed LVEF 5%-10% with severe decrease in right ventricular systolic function. Her serial serum troponin levels were significantly and persistently elevated.

History of past illness

No significant past medical history.

Personal and family history

No cancer or cardiovascular disease in her family.

Physical examination

A 5 cm × 9 cm × 6 cm tumor was noted at the distal right thigh.

Laboratory examinations

Normal complete blood count and comprehensive metabolic panel results.

Imaging examinations

An MRI of the knee showed a 5.6 cm × 9.1 cm × 6.0 cm tumor of the distal right femur, and biopsy revealed high-grade osteoblastic osteosarcoma. Further imaging studies including (18)F-fluorodeoxyglucose positron emission tomography/CT did not indicate distant metastatic disease, and she was referred to medical oncology clinic for

pre-operative chemotherapy. At the time of her pre-treatment evaluation, the patient had no chronic medical issues and was not taking any medications. CT scan of chest showed no evidence of pulmonary metastasis, and baseline transthoracic and dobutamine stress echocardiogram showed normal cardiac function with normal right ventricular systolic function and LVEF 60%-70%.

FINAL DIAGNOSIS

A subsequent autopsy showed no evidence of cancer, and microscopic evaluation of the myocardium was significant for prominent interstitial edema, minimally thinned myocytes, and very focal, minimal interstitial fibrosis (Figure 1).

TREATMENT

She was intubated for acute hypoxic respiratory failure due to cardiogenic shock and started on inotropic and vasopressor support. She subsequently developed cardiorenal syndrome. Due to history of malignancy, she was not a candidate for cardiac transplant. An Impella ventricular assist device was placed emergently through the right femoral artery to increase cardiac output on the seventh day of hospitalization.

OUTCOME AND FOLLOW-UP

After placement of ventricular assist device, she became hemodynamically unstable and unresponsive to fluid resuscitation. A hematoma was noted at right femoral access site with drop in hemoglobin from 8.0 g/dL to 6.3 g/dL. Emergent transfusions were ordered, but the patient decompensated and was found to be pulseless. Advanced cardiac life support was initiated, and bedside echocardiogram showed a pericardial effusion with concern for a cardiac tamponade, so an emergent pericardiocentesis was performed at bedside. Unfortunately, restoration of spontaneous circulation was unable to be obtained and the patient expired.

DISCUSSION

While the rapid onset of the patient's symptoms presented a broad differential diagnosis for her acute heart failure, the lack of evidence for obvious infection, intracardiac malignancy, prior history of coronary artery disease, or cardiac risk factors prompted suspicion for a diagnosis of anthracycline induced cardiotoxicity. This patient had an initial ejection fraction of 70%, which was reduced to 10% in nine months. The echocardiogram did not show apical ballooning, which would be typical for stress or Takutsubo cardiomyopathy. Therefore, patient's cause of death is likely from AIC which may manifest either as early side effect with transient cardiac arrhythmia occurring immediately after first dose, or late side effect with cardiomyopathy occurring 2-3 mo or years after therapy. Most AIC develops within one year after completion of treatment[3]. Early AIC does not lead to subsequent development of cardiomyopathy, and therefore is not considered as an indication to stop anthracycline treatment once cardiac arrhythmia is controlled. The estimated risk of impaired cardiac function is about 1% to 2% at a cumulative dose of 300 mg/m^2 of doxorubicin, and this risk increases significantly to more than 5% when the cumulative dose of doxorubicin exceeds 450 mg/m^2[4].

Retrospective studies and meta-analyses have identified risk factors associated with AIC including: Cumulative dose, administration schedule, duration of infusion, age (> 65 years or < 18 years), female gender, African-American race, history of chest irradiation, use of other cardiac toxic agents such as trastuzumab, existing cardiovascular disease such as coronary artery disease, hypertension and metabolic syndrome[5-7]. Increased risks for AIC have also been associated with genetic polymorphisms in ATP-binding cassette transporter, TOP2 regulator gene *RARG*, uridine diphosphate glucuronosyltransferase 1A6 glucuronidation gene *UGT1A6*, carbonyl reductase genes that reduce anthracyclines to cardiotoxic alcohol metabolites, the myofilament splice variant gene *CELF4*, the hyaluronic acid gene *HAS3*, and

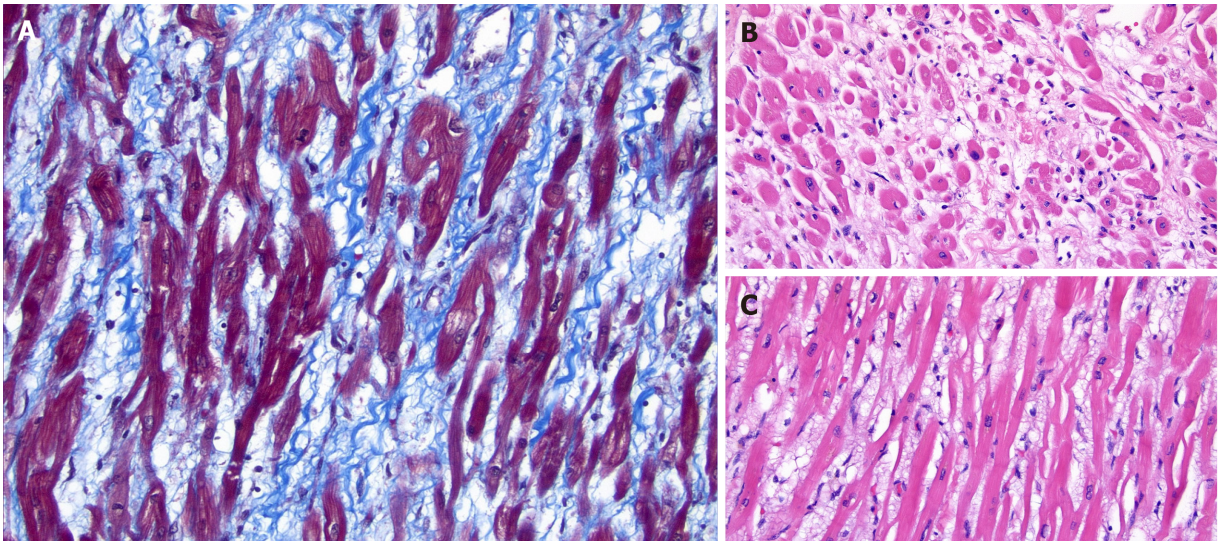

Figure 1 Pathology of myocardium with various stains. A: Trichrome stain showing minimal collagen deposition; B: Cross section of myocardium showing decreased diameter and prominent interstitial edema; C: Hematoxylin and eosin stain showing mildly thinned myocardiocytes with prominent interstitial edema.

rs28714259 from chromosome 15[8-10]. Early identification of patients at risk of AIC is key to preventing cardiotoxicity[11]. We have outlined strategies to mitigate selected modifiable risk factors associated with AIC in Table 1.

Dexrazoxane (ICRF-187) was approved by the United States Food and Drug Administration in 1995 as a cardioprotectant for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and who will continue to receive doxorubicin therapy[12]. In randomized studies, 3% of patients treated with dexrazoxane developed CHF compared with 22% of patients who did not receive dexrazoxane. Its mechanisms of action include reduction of cardiotoxic reactive oxygen species, iron chelation, and catalytic inhibitor of topoisomerase II[13]. It should be noted that there have been some concerns in utilizing this agent due to its side effect of secondary malignancy and decreased antitumor effect of anthracycline[14]. Alterations in infusion schedule and the use of pegylated formulation have also shown to reduce the risk of AIC[15]. A study in pediatric population suggested that infusions greater than 6 h reduce the risk of clinical heart failure when compared to those that received IV pushes[16].

Cardiac monitoring and management of patients receiving anthracyclines have been an area of active research since introduction of these agents in clinical practice and are summarized in Table 2[17-21]. In 2017, the American Society of Clinical Oncology (ASCO) published clinical practice guidelines for the prevention and monitoring of cardiac dysfunction in adult cancer survivors[21]. The ASCO guidelines recommend comprehensive assessment in patients with cancer that includes a history and physical examination, screening for cardiovascular disease risk factors, and an echocardiogram before initiation of anthracycline and other cardiotoxic therapies. Echocardiogram may be performed during cardiotoxic cancer treatment and between 6 mo to 12 mo after completion of therapy in asymptomatic patients considered to be at increased risk for cardiac dysfunction. Patients found to have asymptomatic cardiac dysfunction during routine surveillance should be referred to a cardiologist for further assessment and management.

It is well known that monitoring LVEF alone during anthracycline treatment is insufficient to detect subclinical changes or predict early declines in cardiac function[22]. Studies have shown that persistent elevation of cardiac biomarkers such as troponin and BNP during anthracycline treatment is a harbinger of subsequent LVEF reduction[23,24]. Guidelines from ASCO, European Society for Medical Oncology (ESMO) and Italian Society of Cardiology support periodic measurements of troponin and BNP during anthracycline therapy in patients with risk factors for AIC[18,20,21]. Cardiology consultation and initiation of heart failure therapy with neurohormonal inhibitor such as angiotensin converting enzyme inhibitor (ACE-I) are recommended when cardiac biomarkers are persistently elevated. In addition, these guidelines recommend dexrazoxane treatment, continuous infusion and switching to liposomal formulation in patients planning to receive high-dose anthracyclines (doxorubicin ≥

Table 1 Strategies to mitigate selected modifiable risk factors associated with anthracycline-induced cardiotoxicity

Risk factor	Risk-reduction strategy
Hypertension	Lifestyle modification and pharmacologic control
Diabetes	Lifestyle modification and pharmacologic control
Dyslipidemia	Lifestyle modification and pharmacologic control
Smoking	Smoking cessation
Coronary artery disease	Lifestyle modification and pharmacologic control
Obesity	Lifestyle modification and weight management

Table 2 Monitoring and prevention strategies for anthracycline-induced cardiotoxicity

Method	Description
Biomarkers	Serial measurement of troponin and brain natriuretic peptide
Imaging studies	Regular monitoring of left ventricular function with echocardiogram or cardiac MRI
Pharmacologic agents	Concurrent use of dexrazoxane (for patients receiving doxorubicin ≥ 250 mg/m^2 or epirubicin ≥ 600 mg/m^2)
Administration strategies	Limiting total dose of anthracycline therapy
	Continuous infusion
	Divided doses
	Liposomal formulation

MRI: Magnetic resonance imaging.

250 mg/m^2 or epirubicin ≥ 600 mg/m^2).

Neurohormonal blocking agents such as beta-blockers (BB), ACE-I, angiotensin receptor blockers (ARB), and aldosterone antagonists have been investigated as prevention and treatment of AIC. In preclinical studies, these agents have shown to suppress neurohormonal activation, reduce left ventricular remodeling, and prevent or delay the onset of cardiac symptoms[25]. However, clinical studies have shown mixed results in using neurohormonal inhibitors at the time of chemotherapy to prevent AIC.

The Carvedilol Effect in Preventing Chemotherapy Induced Cardiotoxicity (CECCY; ClinicalTrials.gov Identifier: NCT01724450) phase III trial was the largest BB prevention study which randomized carvedilol *vs* placebo as 1:1 in 192 women with HER2-negative breast cancer receiving doxorubicin 240 mg/m^2 (60 mg/m^2 every 3 wk) with cyclophosphamide followed by paclitaxel[26]. Patients were given incremental dosing of carvedilol or placebo during chemotherapy. The carvedilol group did not meet the primary endpoint which was prevention of early systolic dysfunction within 6 mo of starting doxorubicin. LVEF reduction of at least 10% was noted in 14.5% of the carvedilol group *vs* 13.5% of the placebo group (P = 1.0). Nevertheless, the carvedilol group had lower troponin I levels over 24 wk (P = 0.003) and a lower incidence of LV diastolic dysfunction (P = 0.04). A meta-analysis of 633 patients from 8 randomized trials (including CECCY) comparing carvedilol *vs* placebo to prevent AIC showed significantly reduced rates of low LVEF favoring the carvedilol group (3.2% *vs* 5.8%; OR: 0.42; 95%CI: 0.18-0.99; P = 0.05)[27]. In addition, there were significantly smaller reductions in LVEF in carvedilol-treated patients compared to placebo group.

Prophylactic use of ACE-I to prevent AIC has also been under active investigation. Janbabai *et al*[28] randomized 69 cancer patients receiving enalapril or placebo during doxorubicin treatment of cumulative dose of 365 mg/m^2. The primary end point was change in LVEF measured by echocardiogram from baseline to 6 mo after randomization. There was no change in mean LVEF at 6 mo from baseline in the enalapril treated group, yet there was significant drop in mean LVEF at 6 mo from baseline in control group (46.31% ± 7.04% *vs* 59.61% ± 5.7%; P < 0.001). This study also showed that serum troponin I and creatinine kinase-MB levels were significantly higher 1 mo after the initiation of chemotherapy in the control group than in the enalapril group, suggesting a cardioprotective effect from enalapril. Cardinale *et al*[29]

randomized 114 cancer patients with elevated troponin levels after starting high-dose chemotherapy with either concurrent or prior anthracycline exposure to enalapril *vs* placebo. The primary endpoint was an absolute decrease of more than 10% in LVEF with a decline below 50%, which was prevented in enalapril treatment group when compared with placebo (0% *vs* 43%; $P < 0.001$).

The phase III International Cardio Oncology Society-ONE trial randomized 273 cancer patients taking anthracycline treatment (40% of them receiving median cumulative dose of 240 mg/m^2 doxorubicin) to receive enalapril from initiation of chemotherapy (the prevention group) or during chemotherapy with increased serum troponin level (the troponin-triggered group) (ClinicalTrials.gov Identifier: NCT01968200)[30]. The primary outcome was the incidence of troponin elevation above the threshold at any time during the trial for up to 1 year, and troponin level was measured before and after each anthracycline treatment. There was no difference in the incidence of troponin increase (23% in the prevention *vs* 26% in the troponin-triggered group; $P = 0.50$). Two patients in the prevention and one patient in the troponin-triggered group developed LV dysfunction. This study indicates in patients receiving low cumulative dose of anthracycline, a troponin-triggered strategy to use ACE-I for prevention of AIC seems to be a more convenient and sensible option.

In the OVERCOME phase III trial (ClinicalTrials.gov Identifier: NCT01110824), Bosch *et al*[31] randomized 90 patients with malignant hematologic disorders and normal LVEF in 1:1 ratio to receive either enalapril and carvedilol or nothing during anthracycline therapy. The primary efficacy endpoint was the absolute change from baseline in LVEF, measured by echocardiogram and cardiac MRI at 6 mo after randomization. LVEF did not change in the intervention arm with a median cumulative anthracycline dose of 290 mg/m^2 but significantly decreased in control group with a median cumulative dose of anthracycline of 240 mg/m^2, leading to a -3.1% absolute difference by echocardiography ($P = 0.035$). However, the interventional group did not show any statistically significant reduction in the incidence of heart failure or decreased LVEF > 10% (9.5% *vs* 19%, respectively, $P = 0.22$). The clinical relevance of combined treatment strategy with ACE-I and BB is currently explored in a phase III SAFE trial (ClinicalTrials.gov Identifier: NCT02236806) which uses 2 × 2 factorial design to randomize 480 breast cancer patients[32].

In the PRADA phase II trial (ClinicalTrials.gov Identifier: NCT01434134), Gulati *et al*[33] randomized 120 women with breast cancer receiving adjuvant chemotherapy with epirubicin-based regimen to one of four groups: Candesartan plus placebo, metoprolol plus placebo, candesartan plus metoprolol, and placebo plus placebo. The primary endpoint was change in LVEF measured by MRI after completion of adjuvant treatment. No effect of metoprolol on the overall decline in LVEF was observed. Candesartan group had a smaller mean decline in LVEF than the placebo group (0.8% *vs* 2.6%, $P = 0.03$), indicating prophylactic use of ARB prevents AIC. There are several ongoing large-scale phase II/III randomized clinical trials exploring novel pharmacological intervention in preventing AIC (Table 3). These approaches include hydroxymethylglutaryl-CoA reductase inhibitor (statins) and LCZ696 (neprilysin inhibitor plus angiotensin receptor blocker).

CONCLUSION

Anthracyclines have the potential to exert a direct toxic effect on cardiac myocytes, precipitating symptomatic heart failure. The case presented above demonstrates an example of acute heart failure in a well-compensated young adult who did not, at first glance, warrant greater than routine cardiac surveillance during her treatment course. Most cardiotoxicity after anthracycline-containing therapy occurs within the first year and is associated with the anthracycline dose and LVEF at the end of treatment. Early detection and prompt therapy of cardiotoxicity appear crucial for substantial recovery of cardiac function. When symptoms of heart failure are identified early, discontinuation of anthracycline followed by frequent monitoring of cardiac function can help to alleviate further decline. Yet, when a patient is asymptomatic, it is difficult to predict how often cardiac testing should be done.

While published ASCO recommendations regarding baseline and subsequent cardiac imaging are readily available, there are no clear current consensus for criteria by which to stratify asymptomatic patients who do not fall into the high-risk categories. In patients with cardiovascular risk factors, an increased frequency of cardiac imaging should be considered. As evidence mounts regarding the role of ethnicity or genetic polymorphisms in prognosticating the relative risk of

Table 3 Selected ongoing randomized adult clinical trials on the pharmacological prevention of anthracycline-induced cardiotoxicity

Trial No./phase/name	Patient (*n*) and selection	Randomization schema	Primary endpoint
NCT02236806/Phase III/Cardiotoxicity prevention in breast cancer patients treated with anthracyclines and/or trastuzumab (SAFE)	480 non-metastatic breast cancer receiving anthracycline-based regimens with or without trastuzumab	2 × 2 factorial design. Arm 1: Bisoprolol plus ramipril; Arm 2: Bisoprolol plus placebo; Arm 3: Ramipril plus placebo; and Arm 4: Placebo	Maximum change in left ventricular ejection fraction at months 6, 9, 12 and 24, compared to baseline
NCT03265574/Phase III/Can we prevent chemotherapy-related heart damage in patients with breast cancer? (PROACT)	170 breast cancer receiving epirubicin-based adjuvant chemotherapy	Open-label comparing enalapril versus standard care	Cardiac troponin T release during epirubicin treatment
NCT03760588/Phase II/Prevention of cardiac dysfunction during breast cancer therapy (PRADAII)	300 breast cancer receiving anthracycline-based adjuvant chemotherapy	Double-blinded comparing LCZ696 (neprilysin inhibitor plus angiotensin receptor blocker) versus placebo	Left ventricular ejection fraction at 18 mo
ISRCTN24439460/Phase II/Can heart muscle injury related to chemotherapy be prevented? (cardiac CARE)	168 breast cancer or non-Hodgkin's lymphoma with elevated troponin I level during anthracycline-based chemotherapy	Open-label comparing carvedilol plus candesartan versus standard care	Left ventricular ejection fraction at 6 mo
NCT02943590/Phase II/Statins to prevent the cardiotoxicity from anthracyclines (STOP-CA)	300 newly diagnosed non-Hodgkin's lymphoma receiving doxorubicin-based regimens	Double-blinded comparing atorvastatin versus placebo	Left ventricular ejection fraction at 12 mo
NCT01988571/Phase II/Preventing anthracycline cardiovascular toxicity with statins (PREVENT)	279 breast cancer receiving anthracycline-based adjuvant chemotherapy	Double-blinded comparing atorvastatin versus placebo	Left ventricular ejection fraction at 24 mo

chemotherapy side effects, these risk factors could potentially factor in towards an overall risk assessment and for cardiac monitoring frequency.

Furthermore, while there is evidence that cardioprotective agents such as ACE-I, ARB and BB may help to reduce the severity of LVEF depression following anthracycline exposure, it is not clear whether the observed modest reduction in risk translates to actual reduction in symptomatic heart failure and death. More studies may be needed to explore the utility of cardiac strain markers such as troponin and BNP in identifying early-onset cardiac dysfunction in asymptomatic patients.

Prevention of AIC and cardiovascular toxicities of other anti-cancer therapy requires multidisciplinary approaches such as modification of cardiovascular risk factors, active management of co-morbidities, and pharmacologic therapy in selected patients[34]. The emergence of cardio-oncology program provides opportunities for comprehensive management and in-depth investigation, and is supported by the 2019 American Heart Association Scientific Statement on Cardio-Oncology Rehabilitation to manage cardiovascular outcomes in cancer patients and survivors[35].

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