Takotsubo Syndrome and Inflammatory Bowel Diseases: Does a Link Exist?

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Keywords

Inflammatory bowel diseases · Stress cardiomyopathy · Endothelial dysfunction · Affective disorders · Systemic inflammation

Abstract

Background: Takotsubo syndrome (TTS) is an acute cardiac dysfunction in the absence of viral causes or obstructive coronary disease completely reversible within 4–8 weeks. Inflammatory bowel diseases (IBD) are a group of diseases caused by the interaction between immune system, genetic, and environmental factors against intestinal mucosa. Both these syndromes are characterized by complex mechanisms involving endothelial dysfunction and affective disorders. **Aim:** To assess the possibility of an association between IBD and TTS. **Methods:** First, we present a case of TTS in a patient affected by active stenosing Crohn's disease. Articles in English language were collected from PubMed and Google Scholar

databases with the search terms "takotsubo," "IBD," "crohn disease," "ulcerative colitis". **Results:** Both TTS and IBD show multiple common features: preference for female patients, recurrent course of disease, association with endothelial dysfunction, and affective disorders. Patients affected by IBD could show specific triggers for TTS, such as malabsorption, electrolytes disturbances, and affective disorders. **Conclusions:** Despite pathophysiological similarities between TTS and IBD in active phase, future studies are needed to confirm this apparently possible association and to assess the presence of a pathophysiological link between these diseases.

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Introduction

Takotsubo syndrome (TTS) is an acute cardiac disease presenting by the association of symptoms typical of acute coronary syndrome (ACS), electrocardiographic

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Table 1. International Takotsubo Diagnostic Criteria [4]

1. Transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal or focal wall motion abnormalities
Regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; rare cases of wall motion abnormalities in subtended territory of a single coronary artery (focal TTS)
Right ventricular involvement can be present
2. Emotional, physical, or combined triggers can precede TTS, but this is not obligatory
3. Neurologic disorders (e.g., subarachnoid hemorrhage, stroke/transient ischemic attack, or seizure) as well as pheochromocytoma may serve as trigger for TTS
4. Newly onset ECG abnormalities (ST-segment elevation or depression, T-wave inversion, QTc prolongation); rare cases without ECG changes
5. Moderately elevated cardiac biomarkers levels (troponin, creatine kinase, BNP)
6. Significant coronary artery disease does not exclude TTS
7. No evidence of infectious myocarditis
8. Postmenopausal women predominantly affected

TTS, takotsubo syndrome; ECG, electrocardiogram; BNP, brain natriuretic peptide.

changes, cardiac biomarkers abnormalities, and echocardiographic left ventricular systolic dysfunction (Table 1) [1]. Contrarily to ACS, these alterations are transient and reversible usually within 4–8 weeks.

The term “takotsubo” was first used by Dote et al. [2] and refers to a typical Japanese ceramic pot with a narrow neck and a rounded (*ballooned*) lower portion, similar to the end-systolic shape of the left ventricle (LV), observed in its typical form [3]. Usually – but not necessarily – TTS occurs after a stressful event (physical or psychological), with a significantly higher prevalence in postmenopausal women [4]. Contrarily to ACS, in TTS, coronary angiography does not show hemodynamically significant stenoses. However, the presence of coronary artery disease does not represent an exclusion criterion. Moreover, LV motion abnormalities extending beyond a single coronary artery supply territory and the complete recovery of systolic function after 4–8 weeks represent typical features of TTS [5].

Pathophysiology of TTS, although not completely known, seems related to the cardiac effects of catecholamines, both to an excessive production and to an altered response, possibly due to a polygenic predisposition [4, 6]. Central nervous system (e.g., limbic system, hippocampus, amygdala, hypothalamic-pituitary axis) and autonomic nervous system mediate neuro-hormonal secretion. The excess of catecholamines induces several cardiac effects: (1) direct cardiotoxicity through myocellular hypoxia and free radicals production – this mechanism could be enhanced by electrolytic alterations; (2) subocclusive epicar-

dial coronary spasm; (3) endothelial dysfunction with consequent imbalance between vasodilating and vasoconstricting factors, in favor of the latter – this effect seems to be potentiated by post-menopausal estrogen deficiency; (4) LV ballooning mediated by differences in myocardial regional adrenoceptors' density (β_2 -receptors mostly expressed at apex, while β_1 -receptors and sympathetic nerve endings mostly expressed at basal segments). All these effects contribute to myocardial hypoxia, ventricular stunning, and reduced ejection fraction (EF) [6].

Inflammatory bowel diseases (IBD) are a group of chronic inflammatory disorders targeting the gastrointestinal tract, mainly represented by Crohn's disease (CD) and ulcerative colitis (UC) [7]. Given the unclear etiology, IBD have been erroneously considered as psychosomatic disorders for several years [8]. At present, immune system dysregulation, genetic and environmental factors, and possibly microbiota alterations are considered the main causal mechanisms [9, 10]. However, psychological distress could play a significant role during disease exacerbation [11–13]. Beyond the bowel, IBD show several extraintestinal manifestations including urinary, musculoskeletal, pulmonary, ocular, cutaneous, and cardiac involvement [9, 14]. Pericarditis, myocarditis, endocarditis, valvulopathies, arrhythmias, arterial and venous thromboembolism, Takayasu arteritis, and heart failure represent the most known cardiovascular manifestations [10]. In addition, affective disorders represent a common feature of IBD patients [8].

We present a case of recurrence of TTS in a patient affected by uncontrolled stenosing CD, during hospitalization for malnutrition. In addition, we conducted a search of the available English literature (PubMed and Google Scholar) with the terms “takotsubo,” “IBD,” “Crohn Disease,” “Ulcerative Colitis,” in order to perform a review of this possible association. Written consent was obtained from the patient for case presentation.

Case Presentation

An 81-year-old woman was admitted to our Internal Medicine inpatient unit because of the persistence for several months of abdominal pain, constipation alternating with diarrhea, anorexia, weight loss (about 10 kg), and signs of malnutrition. The patient had a history of hypertension, multinodular thyroid goiter, chronic gastritis, diverticular disease, carotid atherosclerosis, and chronic angioedema urticaria syndrome. She had suffered from recurrent abdominal pain since adolescence, alternating constipation with diarrhea, and for this reason she had been considered a *psychosomatic patient*. However, the patient has never received a psychiatric diagnosis, and she had conducted a normal life with her family. At the age of 73 years old she was finally diagnosed with CD stenosing the distal ileum. Some months after diagnosis, she underwent ileocecal resection because of bowel perforation. At the age of 78 years old, the patient was admitted to a coronary-ICU because of chest pain, dyspnea, electrocardiogram alterations, and raised troponin levels occurred after a quarrel. Echocardiography showed severe left ventricular systolic dysfunction (EF 20–25%) with medio-apical, antero-septal, and lateral wall akinesia. Coronary angiography showed mild coronary atherosclerosis without hemodynamically significant lesions. After acute phase, cardiac rehabilitation program was started with prescription of ranolazine, acetylsalicylic acid, ace-inhibitors, nitrates, spironolactone. About 2 weeks later, an echocardiogram showed a significant improvement of ventricular function with resolution of regional alterations and mild global systolic dysfunction (EF 46%).

At admission to our Department, physical examination revealed normal vital signs, impaired nutritional status (weight 50 kg, height 160 cm, BMI 19.5 kg/m²), and tenderness at palpation of right lower abdominal quadrants. Fasting and parenteral nutrition was prescribed. Blood tests showed hypoalbuminemia, slight elevation of inflammatory markers (CRP, ESR), no electrolytes alterations. During hospitalization, the patient developed chest discomfort: blood pressure was 170/105 mm Hg, pulse rate 54 bpm. A 12-lead electrocardiogram showed sinus bradycardia and T-wave inversion on V2–V6 precordial leads. Troponin levels, initially normal, significantly raised until 2.72 ng/mL (n.v. <0.015 ng/mL) after 12 h. Transthoracic echocardiogram showed severe left ventricular dysfunction (EF 25%) with apical ballooning. Cardiac catheterization did not show hemodynamically significant coronary artery lesions. Supportive treatment was continued, with the addition of enoxaparin. Troponin levels normalized on the eighth day. Patient's diagnostic workup was completed with colonoscopy that showed the presence of a (re)stenosis of the terminal ileum, with 20 cm-length extension at virtual colonoscopy. Histology showed signs of chronic inflammation and granular lesions consistent with recurrence of CD. Treatment with methyl-prednisolone 40 mg/day was started. An echocardiogram performed at day 20th showed normal left ventricular systolic function with complete resolution of apical ballooning. The patient was discharged in improved general status after 24 days of hospitalization with prescription of vedolizumab, steroid tapering-off, aspirin, ramipril, ranolazine, loop diuretic, spironolactone, atorvastatin, beta-blocker, nitrates, and nutritional support.

Discussion

The present case shows the occurrence of chest pain and LV dysfunction without significant coronary lesions in a patient affected by active CD. This association fulfills InterTAK Diagnostic Criteria for TTS [4]. Moreover, evaluating medical history, the previous cardiac event occurred at the age of 78 years old shows criteria for a first episode of TTS, while the one we observed represents a recurrence of TTS, 3 years later. Interestingly, the recurrence of TTS in our patient was concomitant with CD exacerbation. According to literature, TTS recurrence is possible, even if uncommon, with incidence ranging from 1.2% at 6 months to 5% at 6 years. Notably, recurrence can have a different trigger from the first episode [15].

About 90% of TTS occurs in post-menopausal women, after a stressful event [16]. It is conceivable that in our patient the fear for hospitalization and diagnostic workup induced a reactive state of anxiety, precipitating TTS. With this regard, a high prevalence of affective disorders (e.g., anxiety and depression) has been reported both in patients affected by TTS [17] and by IBD [18]. Patients showing anxiety and/or depression frequently show increased norepinephrine response to emotional stress and decreased reuptake of norepinephrine [4]. In these patients, catecholamines' effects are particularly pronounced (e.g., direct myocardial toxicity, epicardial coronary spasm, endothelial dysfunction, and post-ischemic myocardial stunning) [5, 19].

Literature data show a high prevalence of endothelial dysfunction in IBD patients, particularly CD patients, as a result of local and systemic inflammation driven by mucosal damage [20–22]. These pathophysiological mechanisms produce arterial stiffness, early atherosclerosis, and myocardial systolic-diastolic dysfunction [23], accounting for the increased thrombotic burden observed in IBD patients despite a lower prevalence of classical cardiovascular risk factors [23, 24]. Moreover, it seems that drugs modulating bowel inflammation, such as probiotics [25] or infliximab [23], are able to reduce CV risk of IBD patients. Similarly, heparin treatment during active IBD phase is able to modulate the reduction in bowel inflammation [21].

Table 2. Cases of TTS in patients affected by CD, reported in the English literature

	Patient, female	CD, active phase	Comorbidities	Clinical manifestation	Malabsorption	Corticosteroid treatment	Trigger	Other treatment	EKG	LV recovery, days	Recurrence
1	Harle et al. [22], 2011	No	No	pulmonary edema	No	Yes, recently discontinued	Accidental administration of epinephrine	Adalimumab	ST-segment elevation, T-waves inversion	10	No
2	Koeth et al. [27], 2008	No	Hypertension	Chest pain	No	No	Not known	Beta-blockers, ace-inhibitors, aspirin	T-waves inversion	7	Yes
3	Mengoni et al. [25], 2016	Yes	Obesity, DM	Chest pain and dyspnea	Yes	Yes, recently discontinued	Pulmonary embolism, CD exacerbation	NA	T-waves inversion	Few	No
4	Chmielecki et al. [24], 2012	Yes	Intestine tumor	Chest pain	Yes	Yes	CD exacerbation	NA	ST-segment elevation, T-waves inversion, prolonged QT interval	Not reported	No
5	Zegdi et al. [23], 2008	No	Hypertension, breast cancer	Pulmonary edema and hypertension	No	NA	Breast surgery, pheochromocytoma	NA	ST-segment depression	7	No
6	Detweiler et al. [28], 2019	Yes	Depression, hypertension, COPD, DM, neoplasm of adrenal gland, meningioma	Hypotension and lower limb edema	Yes	NA	Depression	vitamina D, diltiazem, thiazide, methyphenidate, mirtazapine, ondansetron, oxycodone	Tachycardia and ST-segment elevation	Not reported	No
7	Emmert et al. [29], 2009	Yes	No	Loss of consciousness	Yes	Yes	CD exacerbation, adalimumab	Azathioprine, adalimumab	Not reported	8	No
8	Moses [30], 2018	Yes	No	Shock	Yes	NA	CD exacerbation	NA	Not reported	14	No
9	Tagami et al. [26], 2016	No	No	Chest pain and dyspnoea	Yes	NA	Depression, eating disorder	No	Sinus tachycardia	Few weeks	No

TTS, takotsubo syndrome; CD, Crohn's disease; LV, left ventricle; NA, not applicable.

Table 3. Cases of TTS in patients affected by UC, reported in the English literature

		Patient, female	UC, active phase	Comorbidities	Case description	Malabsorption	Corticosteroid treatment	Trigger	Other treatment	EKG	LV recovery, days	Recurrence
1	Chatterjee et al. [31], 2018	71	No	No	Chest pain	No	No	No	melasazine	T-waves inversion, prolonged QT interval	28	No
2	Elali et al. [32], 2011	70	No	COPD, osteoporosis	Chest pain, dyspnoea, shock and pulmonary edema	No	NA	Vigorous exercise	NA	ST-segment elevation	22	No
3	Makaryus et al. [33], 2008	47	No	No	Chest pain, shock	No	NA	Psychological stress	No	NA	14	No
4	Rossi [34], 2009	81	No	Arthritis, Grave's disease	Chest pain, presyncope	No	No	Sport, pheochromocytoma	Methimazole, famotidine, estrogen patch	ST-segment elevation, Q wave	3, 8	Yes, 3 year later

TTS, takotsubo syndrome; UC, ulcerative colitis; LV, left ventricle; NA, not applicable.

Similarities between IBD and TTS led us to hypothesize a possible association between these diseases. However, literature data are extremely few. To the best of our knowledge, there are only 13 case reports (Tables 2, 3) describing the occurrence of TTS in IBD patients [26–38]. Interestingly, the totality of reported TTS occurred in female IBD patients. As well as for TTS patients [17, 39], the prevalence of affective disorders is high among IBD patients, particularly among female [18]. Besides the well-known role played by excessive catecholamine release in triggering TTS [26], such as in pheochromocytoma [27], IBD patients, and particularly CD patients, could show disease-specific triggers.

According to Chmielecki et al. [24], malabsorption with consequent electrolytes disturbances could play a pathophysiological role as TTS trigger [28]. Mengoni et al. [25] emphasize the role of disease exacerbation with consequent activation of inflammatory patterns and microvascular dysfunction [29]. According to Zegdi et al. [23] and to Tagami et al. [26], depression and affective disorders could represent specific triggers [27, 30]. Interestingly, 4 out of 9 CD patients presenting with TTS were on treatment with corticosteroids and 5 out of 9 were affected by active CD (Table 2). Finally, some patient did not show any apparent trigger [31].

None of the 4 UC patients with TTS were affected by active disease, neither treated by corticosteroids nor showing malabsorption (Table 3). Thus, it is difficult to find, on the basis of the only 4 reported cases, a specific pathophysiological mechanism for TTS among UC patients [35–38].

Starting from the present case and by reviewing the available literature, TTS and IBD show several similarities: higher prevalence among female patients, recurrent disease course, association with endothelial dysfunction, and affective disorders. However, the possibility of an association between IBD and TTS has never been explored.

During active phase of IBD, intestinal and systemic inflammation plays a pivotal role in the pathogenesis of endothelial and microvascular dysfunction [20, 22, 29]. Endothelial dysfunction represents one of the mechanisms of TTS [4, 6]. The emotional reaction to IBD symptoms and to malnutrition is the mechanism strictly associated to the onset of anxiety and depression during disease activity phase [8, 18]. On this connection, even TTS patients show a higher prevalence of anxiety and depression compared to general population [16, 40], significantly influencing the disease by increasing the concentration of catecholamines [41]. All these mechanisms could trigger TTS in predisposed patients (e.g., female, elderly, with abnormal catecholamine secretion or response, etc.) during active phase of IBD (Fig. 1).

In conclusion, TTS and IBD, particularly CD, share multiple common features. Basing on these aspects, could it be conceivable to consider TTS as an extraintestinal manifestation of IBD, or a consequence of IBD activity in predisposed subjects? Future researches, even based on translational studies in animal models, may be useful to investigate the putative mechanisms that may lead to the possible association between TTS and IBD.

Fig. 1. TTS and IBD: pathophysiological mechanisms highlighting the role of triggers in precipitating TTS and the central role of endothelial dysfunction acting as trade union between the diseases. TTS, takotsubo syndrome; IBD, inflammatory bowel diseases.

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G.A., and S.D.C.: wrote the paper. All authors had access to full text, revised and approved the final version of the manuscript.

Statement of Ethics

The study is consistent with the principles of the Declaration of Helsinki on clinical research involving human subjects and according to the quality standards of Good Clinical Practice. Written informed consent was obtained from the patient.

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Disclosure Statement

Authors declare that no conflict of interest exists.

Author Contributions

A.M., M.M.D.E., S.C., F.B., S.D.C., and C.A.: managed the patient. A.M., M.M.D.E., and G.V., searched for the study rationale and made the research. A.G. and G.A.: participated in the elaboration of literature data. A.M., M.M.D.E., G.V., A.G.,

References

- 1 Y-Hassan S, Tornvall P. Epidemiology, pathogenesis, and management of takotsubo syndrome. *Clin Auton Res*. 2018 Feb;28(1): 53–65.
- 2 Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. [Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases]. *J Cardiol*. 1991;21(2):203–14.
- 3 Sharkey SW, Lesser JR, Maron MS, Maron BJ. Why not just call it tako-tsubo cardiomyopathy: a discussion of nomenclature. *J Am Coll Cardiol*. 2011 Mar;57(13):1496–7.

- 4 Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *Eur Heart J*. 2018 Jun;39(22):2032–46.
- 5 Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *Eur Heart J*. 2018 Jun;39(22):2047–62.
- 6 Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo Syndrome. *Circulation*. 2017 Jun;135(24):2426–41.
- 7 Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. *Annu Rev Immunol*. 2010; 28(1):573–621.
- 8 Addolorato G, Capristo E, Stefanini GF, Gasbarrini G. Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. *Scand J Gastroenterol*. 1997 Oct; 32(10):1013–21.
- 9 Olpin JD, Sjoberg BP, Stilwell SE, Jensen LE, Rezvani M, Shaaban AM. Beyond the Bowel: Extraintestinal Manifestations of Inflammatory Bowel Disease. *Radiographics*. 2017 Jul-Aug;37(4):1135–60.
- 10 Bunu DM, Timofte CE, Ciocoiu M, Floria M, Tarniceriu CC, Barboi OB, et al. Cardiovascular Manifestations of Inflammatory Bowel Disease: Pathogenesis, Diagnosis, and Preventive Strategies. *Gastroenterol Res Pract*. 2019 Jan;2019:3012509.
- 11 Creed F, Craig T, Farmer R. Functional abdominal pain, psychiatric illness, and life events. *Gut*. 1988 Feb;29(2):235–42.
- 12 Helzer JE, Chammas S, Norland CC, Stillings WA, Alpers DH. A study of the association between Crohn's disease and psychiatric illness. *Gastroenterology*. 1984 Feb;86(2):324–30.
- 13 North CS, Clouse RE, Spitznagel EL, Alpers DH. The relation of ulcerative colitis to psychiatric factors: a review of findings and methods. *Am J Psychiatry*. 1990 Aug;147(8):974–81.
- 14 Greuter T, Vavricka SR. Extraintestinal manifestations in inflammatory bowel disease - epidemiology, genetics, and pathogenesis. *Expert Rev Gastroenterol Hepatol*. 2019 Apr; 13(4):307–17.
- 15 Singh K, Carson K, Usmani Z, Sawhney G, Shah R, Horowitz J. Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo cardiomyopathy. *Int J Cardiol*. 2014 Jul;174(3):696–701.
- 16 Nyman E, Mattsson E, Tornvall P. Trigger factors in takotsubo syndrome – A systematic review of case reports. *Eur J Intern Med*. 2019 May;63:62–8.
- 17 Delmas C, Lairez O, Mulin E, Delmas T, Boudou N, Dumontel N, et al. Anxiodepressive disorders and chronic psychological stress are associated with Tako-Tsubo cardiomyopathy- New Physiopathological Hypothesis. *Circ J*. 2013;77(1):175–80.
- 18 Addolorato G, Mirijello A, D'Angelo C, Leggio L, Ferrulli A, Abenavoli L, et al. State and trait anxiety and depression in patients affected by gastrointestinal diseases: psychometric evaluation of 1641 patients referred to an internal medicine outpatient setting. *Int J Clin Pract*. 2008 Jul;62(7):1063–9.
- 19 Rodriguez M, Rzechorzek W, Herzog E, Lüscher TF. Misconceptions and Facts About Takotsubo Syndrome. *Am J Med*. 2019 Jan; 132(1):25–31.
- 20 Principi M, Mastrodonato M, Scicchitano P, Gesualdo M, Sassara M, Guida P, et al. Endothelial function and cardiovascular risk in active inflammatory bowel diseases. *J Crohn's Colitis*. 2013 Nov;7(10):e427–33.
- 21 Day R, Forbes A. Heparin, cell adhesion, and pathogenesis of inflammatory bowel disease. *Lancet*. 1999 Jul;354(9172):62–5.
- 22 Härle T, Kronberg K, Nef H, Möllmann H, Elsässer A. Inverted Takotsubo cardiomyopathy following accidental intravenous administration of epinephrine in a young woman. *Clin Res Cardiol*. 2011 May;100(5): 471–3.
- 23 Zegdi R, Parisot C, Sleilaty G, Deloche A, Fabiani JN. Pheochromocytoma-induced inverted Takotsubo cardiomyopathy: a case of patient resuscitation with extracorporeal life support. *J Thorac Cardiovasc Surg*. 2008 Feb; 135(2):434–5.
- 24 Chmielecki M, Strozzyk A, Jaguszewski M, Gruchala M, Rynkiewicz A. Takotsubo cardiomyopathy related to compound electrolyte aberration and anemia in Crohn's disease. *Int J Cardiol*. 2012 Jun;157(3):e57–9.
- 25 Mengoni A, Cardona A, Ambrosio G. A rare double Trigger for Takotsubo cardiomyopathy. *Intern Med*. 2016;6:1.
- 26 Tagami T, Mertens A, Rothschild D, Chowdhury P. A case of reverse takotsubo cardiomyopathy caused by an eating disorder. *J Cardiol Cases*. 2016 Nov;15(3):77–9.
- 27 Koeth O, Mark B, Zahn R, Zeymer U. Mid-ventricular form of takotsubo cardiomyopathy as a recurrence 1 year after typical apical ballooning: a case report. *Cases J*. 2008 Nov; 1(1):331.
- 28 Detweiler MB, Detweiler JG, Bader GM. Atypical Case of Takotsubo Syndrome in an Elderly Woman. *EC Neurology*. 2019;11:2.
- 29 Emmert MY, Salzberg SP, Emmert LS, Behjati S, Plass A, Felix C, et al. Severe cardiomyopathy following treatment with the tumour necrosis factor-alpha inhibitor adalimumab for Crohn's disease. *Eur J Heart Fail*. 2009 Nov;11(11):1106–9.
- 30 Moses B. A zebra in the sicu: stress cardiomyopathy in a patient admitted for a crohn disease flare. *Crit Care Med*. 2019 Jan;47(1):834.
- 31 Chatterjee D, Philip P, Ling KT. New-onset giant T-wave inversion with prolonged QT interval: shared by multiple pathologies. *Br J Cardiol*. 2018;25:4.
- 32 Elali IM, Missri JC. Takotsubo Cardiomyopathy. *Consultant (00107069)*. 2011;51(8):578–9.
- 33 Makaryus AN, Patrick C, Patcha R, Maccaro P. Cardiac arrest in a patient with normal coronary arteries. *Am J Emerg Med*. 2008 Jul; 26(6):734.e5–7.
- 34 Rossi AP, Bing-You RG, Thomas LR. Recurrent takotsubo cardiomyopathy associated with pheochromocytoma. *Endocr Pract*. 2009 Sep-Oct;15(6):560–2.
- 35 Dias A, Franco E, Mercedes A, Hebert K, Messina D, Quevedo HC. Clinical features of takotsubo cardiomyopathy – a single-center experience. *Cardiology*. 2013;126(2):126–30.
- 36 Nguyen SB, Cevik C, Otahbachi M, Kumar A, Jenkins LA, Nugent K. Do comorbid psychiatric disorders contribute to the pathogenesis of tako-tsubo syndrome? A review of pathogenesis. *Congest Heart Fail*. 2009 Jan-Feb; 15(1):31–4.
- 37 Daniel M, Agewall S, Berglund F, Caidahl K, Collste O, Ekenbäck C, et al. Prevalence of Anxiety and Depression Symptoms in Patients with Myocardial Infarction with Non-Obstructive Coronary Arteries. *Am J Med*. 2018 Sep;131(9):1118–24.
- 38 Gravina AG, Dallio M, Masarone M, Rosato V, Aglitti A, Persico M, et al. Vascular Endothelial Dysfunction in Inflammatory Bowel Diseases: Pharmacological and Nonpharmacological Targets. *Oxid Med Cell Longev*. 2018 Apr;2018:1.
- 39 Triantafyllou C, Nikolaou M, Ikonomidis I, Bamias G, Papaconstantinou I. Endothelial and Cardiac Dysfunction in Inflammatory Bowel Diseases: Does Treatment Modify the Inflammatory Load on Arterial and Cardiac Structure and Function? *Curr Vasc Pharmacol*. 2019 Nov;17(6).
- 40 Papa A, Santoliquido A, Danese S, Covino M, Di Campli C, Urgesi R, et al. Increased carotid intima-media thickness in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2005 Nov;22(9):839–46.
- 41 Di Rienzo DB. Effect of probiotics on biomarkers of cardiovascular disease: implications for heart-healthy diets. *Nutr Rev*. 2014 Jan;72(1):18–29.