Association between ibrutinib and mid-cavitary Takotsubo cardiomyopathy: a case report and a review of chemotherapy-induced Takotsubo’s cardiomyopathy

Dana Elena Giza†, Rohit Moudgil†, Juan Lopez-Mattei, Peter Kim, and Cezar Iliescu*

Department of Cardiology, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Houston, 77030 TX, USA

Received 28 July 2017; accepted 11 October 2017; online publish-ahead-of-print 2 November 2017

Abstract

Takotsubo cardiomyopathy (TC) is a rare but increasingly recognized phenomenon, which can occur as a side effect of cancer treatment. We report an interesting case of a 53-year-old woman with non-small-cell lung cancer, who developed TC after chemotherapy with ibrutinib. Echocardiography revealed marked left ventricular dysfunction with apical hyperkinesis and mid-ventricular hypokinesia. Coronary angiogram was normal but did show mid-cavitary akinesis. To our knowledge, this is the first case of TC with ibrutinib. Therefore, TC remains a rare entity, and we present an elegant case of ibrutinib-mediated mid-cavitary Takotsubo cardiomyopathy with a literature review.

Keywords

Stress-induced cardiomyopathy • Takotsubo • Ibrutinib • Cancer • Case report

Learning points

• Ibrutinib can cause Takotsubo cardiomyopathy.
• Takotsubo cardiomyopathy is under appreciated but a potentially fatal complication. It should be part of differential diagnosis if a patient presents with chest pain. Prompt management is central to successful outcomes. This also entails discontinuation of current chemotherapy for successful cardiac recovery.

Introduction

Takotsubo cardiomyopathy (TC) has been reported with high incidence in cancer patients, in the absence of obstructive coronary artery disease (CAD).1,2 Several classes of chemotherapeutic agents that are known to be cardiotoxic were found to be associated with TC in cancer patients.3-5 First association between small-molecule tyrosine kinase inhibitors (TKIs) and TC has been made in a cancer patient undergoing treatment with axitinib; however, there are no other reports describing this association in cancer patients undergoing chemotherapy with other TKIs. In this case report, we describe a 53-year-old woman who developed mid-cavitary TC in the context of receiving ibrutinib. Ibrutinib is a small-molecule TKI that selectively and irreversibly inhibits both Bruton’s tyrosine kinase (Btk) and epidermal growth factor receptor (EGFR).6 The most commonly encountered cardiovascular adverse effects of ibrutinib are hypertension and cardiac rhythm abnormalities (atrial fibrillation and/or atrial flutter), but no TC episodes have been linked by now to ibrutinib administration.

* Corresponding author. Tel: +7 13 792 6242, Fax: +7 13 745 1942, Email: ciliescu@mdanderson.org. This case report was reviewed by Nisha Mistry, Christian Jøns, and Nikolaos Bonaros.
† The first two authors are co-authors.
Case presentation

A 53-year-old Asian woman, without known pre-existing cardiovascular risk factors, presents with mid-sternal chest pain, 3 weeks after the initiation of ibrutinib therapy (560 mg daily for a cycle of 28 days) as salvage therapy for non-small-cell carcinoma. She was initially diagnosed with non-small-cell lung cancer in 2011, when it was also discovered that she had endometrial carcinoma (hysterectomy for endometroid adenocarcinoma FIGO Grade II). Subsequently, the patient underwent right upper lobectomy for the non-small-cell cancer (T3N1M0, EGFR positive), followed by chemotherapy with erlotinib and bevacizumab, which resulted in disease progression with metastases to the spine, bones, adrenal glands, and lungs. Ibrutinib monotherapy was then recommended as salvage therapy. Please note her Eastern Cooperative Oncology Group status was 1 at the time of initiation of the ibrutinib therapy. Within 3 weeks after starting ibrutinib, the patient experienced chest pain, described as ‘pressure-like’, moderate to severe in intensity that started 7 days prior to hospital presentation and was progressively worsening. She also reported having decreased exercise tolerance and increased tiredness since the initiation of ibrutinib treatment. There were no emotional triggers (grief, anxiety, or anger) documented in the clinical notes before/during TC event; no clinical signs of systemic infection or pericarditis; and no major surgical procedures or intubation at the time of the TC episode. No other drug, administered concomitant or pericarditis; and no major surgical procedures or intubation at the time of the TC episode. No other drug, administered concomitant with ibrutinib, that is known to trigger TC, was identified. Of note, the only medications patient was maintained on during ibrutinib treatment were ondansetron for nausea, lorazepam as a sleeping aid, and tramadol for pain secondary to bony metastases.

Physical examination revealed the patient with general fatigue and malaise. Cardiac auscultation revealed presence of S1, S2, and S4 with no murmurs noted. She had rales bilaterally at the base. The rest of the physical examination was unremarkable.

A 12-lead electrocardiogram revealed significant ST elevation in leads V2 and V3 and T-wave inversion in leads V1 through V3 (with no murmurs noted. She had rales bilaterally at the base. The rest of the physical examination was unremarkable.

Laboratory results showed elevated cardiac enzyme values, including a TnI level of 0.65 ng/mL (normal range <0.03 ng/mL) and a creatine kinase MB level of 12.7 ng/mL (normal range 0.06–6.3 ng/mL). Chest X-ray showed non-specific bilateral ground-glass opacities and small consolidations with minimal pleural effusions, interpreted in the context of her primary disease, and no signs of pericardial effusion. Transthoracic echocardiogram showed apical hyperkinesis and mid-ventricular hypokinesia and estimated the left ventricular ejection fraction (LVEF) to be 25%. The patient was monitored for haemodynamic instability, received clopidogrel (300 mg), aspirin (81 mg daily), and intravenous heparin (5000 IU), and underwent left-sided cardiac catheterization with coronary angiography that showed no obstructive CAD. Left ventriculography identified basilar and apical hyperkinesis and mid-ventricular hypokinesia (mid-cavity) (Figure 2). Please note that traditional TC was described as akinesis to dyskinesia localized in the apex. Given the clinical presentation, elevation of cardiac biomarkers without angiographic evidence of CAD or spasm, mid-cavity Takotsubo was considered. The patient was managed medically with the administration of furosemide (20 mg daily) and carvedilol (6.25 mg twice daily), while the ibrutinib treatment was stopped. A follow-up echocardiographic study done 4 days later showed normalized ejection fraction (LVEF = 55%), which allowed the patient to continue cancer therapy (palliative radiotherapy). Treatment with ibrutinib was not restarted again after the event. The patient remained asymptomatic and had no reoccurrence of Takotsubo episodes.

Discussion

Takotsubo cardiomyopathy in cancer patients has the same features as in the general population, occurring more commonly in post-menopausal women (median age 61 years) with minimal cardiac risk factors.7–10 The proposed pathogenic mechanisms of TC in cancer patients include microvascular vasospasm induced by catecholamines, inadequate increase in cardiac sympathetic nervous activity, modification of cardiac adreno receptors sensitivity by the underlying malignancy, and oestrogen reduction.11,12 Adverse chemotherapy events of the antineoplastic agents, such as 5-fluorouracil, capetabine, sorafenib, and bevacizumab, trigger TC in cancer patients.13–16 There are only 29 reports published by now on Takotsubo occurrence during cancer treatment (Table 1), among which there are only 2 case reports on mid-cavitary TC. Khanji et al.24 suggested a first association between mid-cavitary TC and trastuzumab in a patient with breast cancer, a monoclonal antibody against HER-2, which interferes with normal growth, repair, and survival of cardiomyocytes. In addition, Burty et al.32 described a case in which administration of trastuzumab in a patient with breast cancer after heart failure secondary to postoperative TC had not caused any heart-related symptoms.

To our knowledge, this is a unique presentation of mid-cavitary hypokinesia occurring in a cancer patient treated with ibrutinib. Ibrutinib has been shown to affect EGFR-mutant non-small-cell lung cancer cell lines through the EGFR signalling pathway.39 Inhibition of the EGFR pathway decreases the production of tumour-derived and tumour-derived vascular endothelial growth factor (VEGF), which acts on endothelial cells to promote angiogenesis.40 White et al.41 proposed that inhibition of VEGF decreases endothelial nitric oxide synthase levels and nitric oxide release, attenuating endothelial cell proliferation, vascular permeability, and angiogenesis. While it may hold true for the previously described case of Takotsubo associated with a small-molecule TKI (axitinib), which selectively inhibits VEGF, the onset of the symptoms was 24 h after the initial exposure, and our

| Timeline | Events |
|----------|--------|
| Time 0 | Initiation of Ibrutinib |
| 3 Weeks | Start of Chest Pain |
| 7 days later | Echocardiogram |
| | Cardiac Catheterization |
| | Diagnosis: Takotsubo's Cardiomyopathy |
| | Stopping Ibrutinib |
| 4 days later | Initiation of lasix and carvedilol |
| | Repeat Echocardiogram |
Figure 1 Twelve-lead ECG on presentation with significant ST elevation in leads V2 and V3 and T-wave inversion in leads V1 through V3 in a 53-year-old woman with mid-cavitary stress-induced cardiomyopathy after ibrutinib treatment.

Figure 2 Coronary angiography of the left coronary tree (A) and of the right coronary tree (B) with no angiographic evidence of obstructive disease. Left ventriculogram showing apical and basal hyperkinesis and mid-cavitary akinesis in systole (C) and diastole (D).
| Authors (year) | Age and gender | Cancer | Trigger event | ECG | Cath results | Wall motion | LVEF during the acute phase (%) | LVEF at recovery (%) | Complications |
|----------------|----------------|--------|---------------|-----|--------------|-------------|---------------------------------|----------------------|---------------|
| Antimetabolite anti-neoplastic agents | | | | | | | | | |
| Gianni et al.17 (2009) | 79 W | Colon | 5-Fluorouracil (10th cycle) | ST elevation | Presence of CAD | Apical | 34 | 70 (4 weeks) | NA |
| Kobayashi et al.18 (2009) | 62 W | Rectal | 5-Fluorouracil (6th cycle) | ST elevation | Normal coronary arteries | Apical | 28 | 67 (10 days) | NA |
| Basselin et al.4 (2011) | 48 M | Colon | 5-Fluorouracil (1st cycle) | ST depress and T-wave inversion | Normal coronary arteries | Apical | 15 | Recovery (1 month) | IABP, pressor |
| Grunwald et al.19 (2012) | 60 W | Colon | 5-Fluorouracil (1st cycle) | ST elevation | 30–40% LAD | Apical | 15–20 | 55–60 (4 weeks) | NA |
| Lim et al.16 (2013) | 66 W | Rectal | 5-Fluorouracil (3rd cycle) | T-wave inversion | No flow-limiting stenosis | Apical | 30 | Improved LV function (10 days) | LV thrombus and embolic stroke |
| Ozturk et al.20 (2013) | 48 M | Gastric cancer | 5-Fluorouracil (1st cycle) | T-wave inversion | Non-obstructive CAD | Apical | 15 | 50 (27 days) | VT/VF, respiratory failure |
| Baumann et al.5 (2014) | 58 M | AML | Cytarabine (2nd cycle) | T-wave inversion | Normal coronary arteries | Apical | 20 | 55 | Cardiogenic shock |
| Stewart et al.13 (2010) | 81 W | Colon | Capecitabine (1st cycle) | T-wave inversion | 30% RCA | Apical | 35 | 60 (1 week) | NA |
| Qasem et al.21 (2014) | 47 W | Breast | Capecitabine (1st cycle) | ST elevation and T-wave inversion | Non-obstructive CAD | Apical | 30 | 55 (6 weeks) | NA |
| Antiangiogenic antineoplastic agents | | | | | | | | | |
| Franco et al.15 (2008) | 76 M | Colon | Bevacizumab (1st cycle) | ST elevation | Non-critical LM | Apical | NA | Recovery LV function (3 weeks) | NA |
| Franco et al.15 (2008) | 61 M | Lung | Bevacizumab (2nd cycle) | ST elevation | Non-obstructive CAD | Apical | NA | Recovery LV function | NA |
| Numico et al.14 (2012) | 57 W | Renal | Sunitinib | ST elevation | Non-obstructive CAD | Apical | 15–20 | 68 (3 months) | LV thrombus |
| Ovadia et al.23 (2015) | 71 W | RCC | Axitinib | ST elevation | Non-obstructive CAD | Apical | 20–25 | 50–55 (3 weeks) | NA |
| Bhakta et al.23 (2009) | 71 W | Thyroid | Combretastatin (1st cycle) | T-wave inversion | No flow-limiting stenosis | Apical | 40–50 | 55–65 (1 month) | NA |
| HER2/neu receptor inhibitor | | | | | | | | | |
| Khanji et al.24 (2013) | 50 W | Breast | Trastuzumab (11th cycle) | T-wave inversion | Normal coronary arteries | Mid-cavity | NA | LV function normalized (6 weeks) | NA |

Continued
| Authors (year) | Age and gender | Cancer | Trigger event | ECG | Cath results | Wall motion | LVEF during the acute phase (%) | LVEF at recovery (%) | Complications |
|---------------|----------------|--------|---------------|-----|--------------|------------|---------------------------------|---------------------|---------------|
| Monoclonal antibody | | | | | | | | | |
| Smith and Auseon | 60 W | Lymphoma | Rituximab | ST elevation | Non-obstructive CAD | Apical | 20–25 | 42 (1 month) | NA |
| Ng et al. (2015) | 66 M | Leukaemia | Rituximab | ST elevation | Non-obstructive CAD | Apical | 40 | NA | NA |
| Geisler et al. (2015) | 83 W | Melanoma | Ipilimumab (4th cycle) | ST elevation | 30% LAD | Apical | 50 | NA | Transient SVT and VT |
| Immunological therapy | | | | | | | | | |
| Damodaran et al. (2014) | 55 W | Melanoma | Interleukin-2 | T-wave inversion | Normal coronary arteries | Apical | 45 | 65 | NA |
| Others | | | | | | | | | |
| Gangadhar et al. (2008) | 64 W | Oesophageal cancer | Endoscopic stent placement | ST elevation | Normal coronary arteries | Apical | Severely reduced | Marked improved (6 days) | Intubation |
| Toyooka et al. (2012) | 72 M | Lung | Lung resection | T-wave inversion | 75% RCA | Apical | 30 | Improved LV function (19 days) | NA |
| Hope et al. (2013) | 53 W | Ovarian cancer | Intraperitoneal port placement | ST elevation | Non-obstructive CAD | Apical | 15–20 | NA | IABP, HIT, DIC, haemorrhagic stroke |
| Burgy et al. (2014) | 40 W | Breast | Lumpectomy | Sinus tachycardia | Normal coronary arteries | Mid-cavity | 45 | 57 (NA) | NA |
| Joo et al. (2011) | 64 W | Liver cancer | Radio frequency ablation | ST elevation and Q wave | Normal coronary arteries | Apical | 34 | 70 | VT |
| Lee et al. (2011) | 51 M | Lung cancer | Lung resection | ST elevation | 30% LAD | Apical | Severe dysfunction | Normal | Cardiac arrest and bradycardia |
| Guerrero et al. (2009) | 77 M | Oesophageal cancer | Bronchial stent placement | Normal sinus rhythm | Normal coronary arteries | Apical | 15 | 55 | Cardiogenic shock |
| Modi and Baig (2009) | 66 W | Breast | Radiation | T-wave inversion | Normal coronary arteries | Apical | NA | NA | NA |
| Schweizer et al. (2011) | 69 W | Laryngeal cancer | Clogged jejunostomy | ST elevation | Non-obstructive CAD | Apical | 35–40 | Normal | Hypotension |
| Singh et al. (2014) | 59 W | Lung | Pain crisis | ST elevation | Normal coronary arteries | Apical | 35% | NA | NA |
patient developed symptoms after 3 weeks of exposure to ibritinib.22
Alternatively, ibritinib is a Btk inhibitor.42 Bruto’s tyrosine kinase contains a
Pleckstrin Homology domain that binds phosphatidylinositol (3,4,5)-trisphosphate (PIP3). This PIP3 binding induces Btk to
phosphorylate phospholipase C, which in turn hydrolyses phosphati-
dylinositol-4, 5-bisphosphate, a phosphatidylinositol, into two second
messengers, inositol triphosphate (IP3) and dicygiclycerol (DAG),
which in turn activates protein kinase C.13 Ibritinib inhibits PKC (via
inhibition of Btk), which may lead to increased L-type calcium
activity,44 the latter implicated in increased myocardial contractility.45
This may be a cause for TC in this patient; however, it is speculative at
this point and needs further investigation to verify it.
Takotsubo cardiomyopathy in cancer patients presents with symp-
oms of myocardial ischaemia and specific changes in electrophysi-
ographic, echocardiographic, and cardiac angiographic examinations.
Electrocardiogram commonly shows ST-segment elevation, followed
by T-wave inversion in precordial leads; the cardiac enzymes are typi-
cally elevated; and echocardiography usually reveals hypokinesis, dys-
kinesis, or akinesis of the left ventricle, which usually involves the
 apex but can also include the mid-ventricular and basal segments.1
The regional wall motion abnormalities usually extend beyond a sin-
gle epicardial vascular distribution; however, a rare focal variant that
is usually confined to the anterolateral segment of the left ventricle
has been described.46 In the case of our patient, mid-ventricular seg-
ment was involved, showing hyperkinesis of apical and basal ventricu-
lar segments. Patients with TC also show abnormal global and
regional myocardial strain patterns that improve over time.47
Patients with TC generally have a favourable prognosis, although
serious complications (e.g. cardiogenic shock or malignant arrhyth-
mia) have been reported.48 The management of TC largely consists
of the patient in line with COPE guidance.

Conflict of interest: The authors have no conflicts of interest or
financial disclosures to declare. All procedures performed in the
studies involving human participants were in accordance with the
ethical standards of the institutional and/or national research com-
mittee and with the 1964 Helsinki declaration and its later amend-
ments or comparable ethical standards.

References
1. Madsen M, Prasad A. Proposed Mayo Clinic criteria for the diagnosis of Tako-
Tsубo cardiomyopathy and long-term prognosis. Herz 2010; 35:240–243.
2. Prasad A. Apical ballooning syndrome: an important differential diagnosis of
idioventricular cardiomyopathy. Clin Cardiol 2007; 30:456–459.
3. Qasem A, Bin Abdulhak AA, Aly A, Moormeier J. Capcetabine-induced
Takotsubo cardiomyopathy: a case report and literature review. Am J Ther 2016.
23:e1188–e1192.
4. Basselin C, Fontanges T, Descotes J, Chevalier P, Bui-Xuan B, Fenard G, Timour
Q. 5-Fluorouracil-induced Tak-Tsubo-like syndrome. Pharmacotherapy 2011;
31:506–512.
5. Baumann S, Huseynov A, Goranova D, Faust M, Behnes M, Nothe F, Heidenreich
D, Hofmann W-K, Borggreve M, Akin I, Klein S. Takotsubo cardiomyopathy after
systemic consolidation therapy with high-dose intravenous cytarabine in a patient
with acute myeloid leukemia. Oncl Res Treat 2014;37:487–490.
6. Homberg LA, Smith AM, Sirisawad M, Verner E, Loury D, Chang B, Li S, Pan Z,
Thamm OH, Miller RA, Buggy J. The Bruton tyrosine kinase inhibitor PCI-32765
blocks β-cell activation and is efficacious in models of autoimmune disease
and B-cell malignancy. Proc Natl Acad Sci U S A 2010; 2010:13075–13080.
7. Hurst RT, Prasad A, Askew JW 3rd, Sengupta PP, Tajik AJ. Takotsubo cardiomy-
opathy: a unique cardiomyopathy with variable ventricular morphology. JACC
Cardiovasc Imaging 2010;3:641–649.
8. Akgün I, Salihoğlu YS, Sayın MR, Eri T, Karabag T, Dogan SM, Aydin M.
Tirofiban in Takotsubo cardiomyopathy. Atypical broken heart syndrome with
extremely fast recovery: a case report. Herz 2013;38:89–92.
9. Azzarelli S, Amico F, Galassi AR, Giacoppo M, Fiscella A. A case of transient
left mid ventricular ballooning. J Cardiovasc Med 2007;8:629–632.
10. Munoz E, Iliescu G, Veqongpa P, Chchantak S, Karimzad K, Lopez-Matte J, Yusuf
DW, Marmagikal K. Takotsubo Stress Cardiomyopathy. “Good news” in Cancer
Patients? J Am Coll Cardiol 2016;68:1143–1144.
11. Hinojosa-Laborde C, Chapa I, Lange D, Haywood JR. Gender differences in symp-
pathetic nervous system regulation. Clin Exp Pharmacol Physiol 1999;26:122–126.
12. Taddese S, Virdis A, Ghisodani L, Mattei P, Sudano I, Bernini G, Pinto S, Salveti A.
Menopause is associated with endothelial dysfunction in women. Hypertension
1996;28:576–582.
13. Stewart T, Pavlakis N, Ward M. Cardiotoxicity with 5-fluorouracil and capeci-
bine: more than just vasospastic angina. Intern Med J (2010);40:303–307.
14. Numico G, Silvastrelli N, Mozzaardfredo A, Torgo A, Malloisi A, Cristofano A, Thiebat B. Takotsubo syndrome in a patient treated with sunitinib for renal cancer. J Clin Oncol 2012;30:e218–e220.
15. Franco TH, Khan A, Jashi V, Thomas B. Takotsubo cardiomyopathy in two men
receiving bevacizumab for metastatic cancer. Ther Clin Risk Manag 2006;2:1367–70.
16. Lim SH, Wilson SM, Hunter A, Hill J, Beale P. Takotsubo cardiomyopathy and 5-
Fluorouracil: getting to the heart of the matter. Case Rep Oncol Med 2013;
2013:206765.
17. Gianni M, Dentali F, Lonn E. 5-Fluorouracil-induced apical ballooning syndrome:
A case report. Blood Coagul Fibrinolysis 2009;20:306–308.
18. Kobayashi N, Hata N, Yokoyama S, Shindai T, Shinkade A, Mizuno K. A case of
Takotsubo cardiomyopathy during 5-fluorouracil treatment for rectal adenocar-
cinoma. Nippon Med Sch 2009;76:27–33.
19. Grumwald MR, Howie L, Diaz LA Jr. Takotsubo cardiomyopathy and fluorouracil:
case report and review of the literature. J Clin Oncol 2012;30:e11–e14.
20. Ozturk MA, Ozveren O, Cinar V, Erdik B, Oyan B. Takotsubo syndrome: an
undiagnosed complication of 5-fluorouracil mimicking acute myocardial
infarction. Blood Coagul Fibrinolysis 2013;24:90–94.
21. Qasem A, Bin Abdulhak AA, Aly A, Moormeier J. Capecitabine-induced takot-
subo cardiomyopathy: a case report and literature review. Am J Ther 2016;
23:e1188–e1192.
22. Ovadia D, Esquenazi Y, Bucay M, Bachir CR. Association between takotsubo
cardiomyopathy and axtinib: case report and review of the literature. J Clin Oncol
2015;33:e1–e3.
23. Bhakta S, Flisk MM, Cooney MM, Greskovich JF, Gilkeson RC, Remick SC, Ortiz J.
Myocardial stunning following combined modality combretastatin-based chemo-
therapy: two case reports and review of the literature. J Clin Cardiol 2009;32:
280–284.
24. Khan M, Nolan S, Gwynne S, Pudney D, Ionescu A. Tak-Tsubo syndrome after
trastuzumab—an unusual complication of chemotherapy for breast cancer. Clin
Oncol (R Coll Radiol) 2013;25:329.
25. Smith SA, Auseon AJ. Chemotherapy-induced takotsubo cardiomyopathy. Heart
Fail Clin 2013;9:233–242.
26. Ng KH, Dearden C, Gruber P. Rituximab-induced Takotsubo syndrome: more
cardiotoxic than it appears! BMJ Case Rep 2015;doi:10.1136/bcr-2014-208203.
27. Geider BP, Raad RA, Eissan D, Sharon E, Schwartz DR. Apical ballooning and
cardiomyopathy in a melanoma patient treated with ipilimumab: a case of
takotsubo-like syndrome. J Immunother Cancer 2015;3:4.
28. Damodaran S, Mrozek E, Liebner D, Kendra K. Focal takotsubo cardiomyopathy with high-dose interleukin-2 therapy for malignant melanoma. *J Natl Compr Canc Netw* 2014;12:1666–1670. quiz 70.

29. Gangadhar TC, Von der Lohe E, Sawada SG, Helft PR. Takotsubo cardiomyopathy in a patient with esophageal cancer: a case report. *J Med Case Rep* 2008;2:379.

30. Toyooka S, Akagi S, Furukawa M, Nakamura K, Soh J, Yamane M, Ota T, Miyoshi S. Takotsubo cardiomyopathy associated with pulmonary resections after induction chemoradiotherapy for non-small cell lung cancer. *Gen Thorac Cardiovasc Surg* 2012;60:599–602.

31. Hope E, Smith M, Zeligs K, Hamilton CA, Miller C. Takotsubo cardiomyopathy following laparoscopic port placement in a patient with ovarian cancer. *Gynecol Oncol Case Rep* 2013;3:16–17.

32. Burgy M, Brossat H, Barthelemy P, Imperiale A, Trinh A, Hazam CA, Bergerat JP, Mathelin C. First report of trastuzumab treatment after postoperative Takotsubo cardiomyopathy. *Anticancer Res* 2014;34:3579–3582.

33. Joo I, Lee JM, Han JK, Choi BI, Park EA. Stress (tako-tsubo) cardiomyopathy following radiofrequency ablation of a liver tumor: a case report. *Cardiovasc Intervent Radiol* 2011;34:586–589.

34. Lee S, Lim SP, Yu J-H, Na MH, Kang S-K, Kang M-W, Oh HK. Stress-induced cardiomyopathy during pulmonary resection (Takotsubo syndrome): a case report. *Korean J Thorac Cardiovasc Surg* 2011;44:294–297.

35. Guerrero J, Majid A, Ernst A. Cardiogenic shock secondary to Takotsubo syndrome after debridement of malignant endobronchial obstruction. *Chest* 2009;135:217–220.

36. Modi S, Baig W. Radiotherapy-induced Takotsubo cardiomyopathy. *Clin Oncol (R Coll Radiol)* 2009;21:361–362.

37. Schweizer MT, Mehta R, Salgia R, Villafar VM. Takotsubo cardiomyopathy in a patient with squamous cell esophageal carcinoma. *J Clin Oncol* 2011;29:e598–e600.

38. Singh SB, Harle IA. Takotsubo cardiomyopathy secondary in part to cancer-related pain crisis: a case report. *J Pain Symptom Manage* 2014;47:137–142.

39. Gao W, Wang M, Wang L, Lu H, Wu S, Dai B, Ou Z, Zhang L, Heymach JV, Gold KA, Minna J, Roth JA, Hofstetter WL, Swisher SG, Fang B. Selective antitumor activity of ibrutinib in EGFR-mutant non-small cell lung cancer cells. *J Natl Cancer Inst* 2014;106.

40. Larsen AK, Oualet D, El Ouadrani K, Petitprez A. Targeting EGFR and VEGF(R) pathway cross-talk in tumor survival and angiogenesis. *Pharmacol Ther* 2011;131:80–90.

41. White AJ, LaGerche A, Toner GC, Whitbourn RJ. Apical ballooning syndrome during treatment with a vascular endothelial growth factor receptor antagonist. *Int J Cardiol* 2009;131:e92–e94.

42. Pan Z, Scheerens H, Li SJ, Schultz BE, Sprengeler PA, Burnil LC, Mendonca RV, Sweeney MD, Scott KCK, Grothaus PG, Jeffery DA, Spoerke JM, Honigberg LA, Young PR, Dairaumple SA, Palmer JT. Discovery of selective irreversible inhibitors for Bruton’s tyrosine kinase. *ChemMedChem* 2007;2:58–64.

43. Seda V, Mraz M. B-cell receptor signalling and its crosstalk with other pathways in normal and malignant cells. *Eur J Haematol* 2015;94:193–205.

44. McHugh D, Sharp EM, Scheuer T, Catterall WA. Inhibition of cardiac L-type calcium channels by protein kinase C phosphorylation of two sites in the N-terminal domain. *Proc Natl Acad Sci U S A* 2000;97:12334–12338.

45. Bodi I, Mikula G, Koch SE, Akhter SA, Schwartz A. The L-type calcium channel in the heart: the best goes on. *J Clin Invest* 2005;115:3306–3317.

46. Bybee KA, Kara T, Prasad A, Lerman A, Barsness GW, Wright RS, Rihal CS. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med* 2004;141:858–865.

47. Hegemann F, Weiss C, Hamm K, Kaden J, Sussbeck T, Papavassiliu T, Borgia M, Hagi D. Global and regional myocardial function quantification by two-dimensional strain in Takotsubo cardiomyopathy. *Eur J Echocardiogr* 2009;10:760–764.

48. Rademakers LM, Weijers RW, Wijnbergen IF. Transient midventricular ballooning syndrome. an atypical presentation of takotsubo cardiomyopathy. *Acta Cardiol* 2011;66:811–813.

49. Sachin KAJ, Hrishabh M, Larsen T, Shukri D. Mid-ventricular takotsubo: a case report. *JCIR* 2013;4:452–456.