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CASE REPORT

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

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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.

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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 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 V_2 and V_3 and T-wave inversion in leads V_1 through V_3 (*Figure 1*). 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-cavitary) (*Figure 2*). Please note that traditional TC was described as akinesis to dyskinesis localized in the apex. Given the clinical presentation, elevation of cardiac biomarkers without angiographic evidence of CAD or spasm, mid-cavitary 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 ibrutnib was not restarted again after the event. The patient remained asymptomatic and had no reoccurrence of Takotsubo episodes.

Timeline

Time	Events
Time 0	Initiation of Ibrutinib
3 Weeks	Start of Chest Pain
7 days later	Echocardiogram
	Cardiac Catherterization
	Diagnosis: Takotsubo's Cardiomyopathy
	Stopping Ibrutinib
	Initiation of lasix and carvedilol
4 days later	Repeat Echocardiogram

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, capecitabine, 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, Burgy *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 non-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

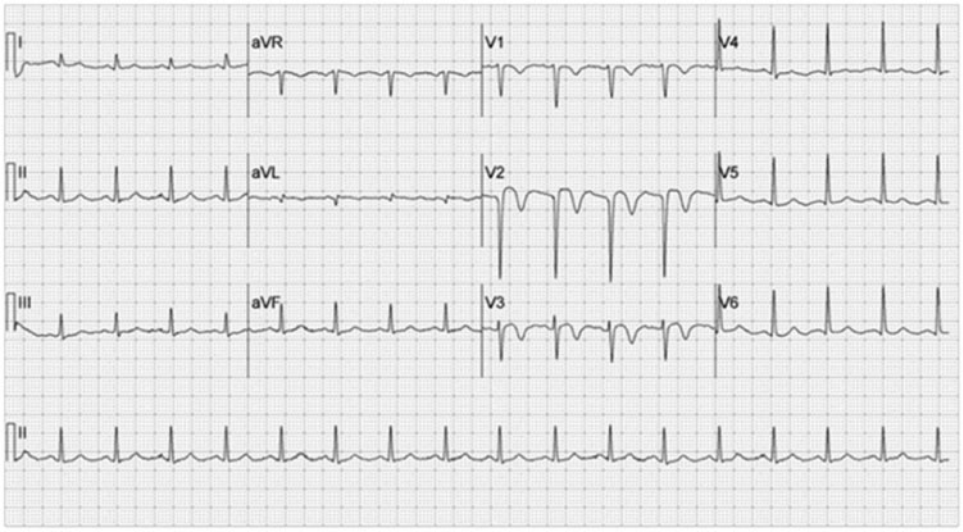

Figure 1 Twelve-lead ECG on presentation with significant ST elevation in leads V_2 and V_3 and T-wave inversion in leads V_1 through V_3 in a 53-year-old woman with mid-cavitary stress-induced cardiomyopathy after ibrutinib treatment.

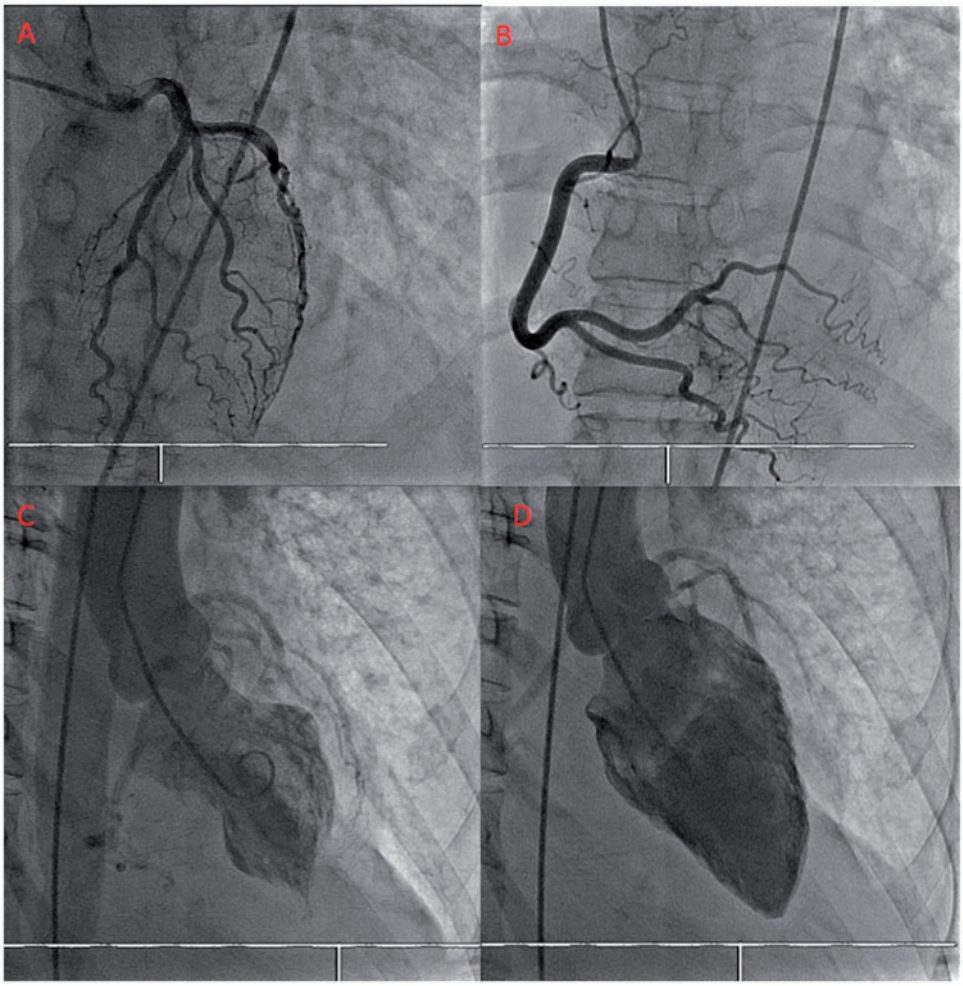

Figure 2 Coronary angiography of the left coronary tree (*A*) and of the right coronary tree (*B*) with no angiographic evidence of obstructive disease. Left ventriculogram showing apical and basal hyperkinesis and mid-cavitary akinesis in systole (*C*) and diastole (*D*).

Table I Case reports on stress-induced cardiomyopathy in cancer patients

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[a]	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[b]	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-Flurouracil (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.*[22] (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

Table I *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[25] (2013)	60 W	Lymphoma	Rituximab	ST elevation	Non-obstructive CAD	Apical	20–25	42 (1 month)	NA
Ng *et al.* (2015)[26]	66 M	Leukaemia	Rituximab	ST elevation	Non-obstructive CAD	Apical	40	NA	NA
Geisler *et al.*[27] (2015)	83 W	Melanoma	Ipilimumab (4th cycle)	ST elevation	30% LAD	Apical	50	NA	Transient SVT and VT
Immunological therapy									
Damodaran *et al.*[28] (2014)	55 W	Melanoma	Interleukin-2	T-wave inversion	Normal coronary arteries	Apical	45	65	NA
Others									
Gangadhar *et al.*[29] (2008)	64 W	Oesophageal	Oesophageal stent placement	ST elevation	Normal coronary arteries	Apical	Severely reduced	Marked improved (6 days)	Intubation
Toyooka *et al.*[30] (2012)	72 M	Lung	Lung resection	T-wave inversion	75% RCA	Apical	30	Improved LV function (19 days)	NA
Hope *et al.*[31] (2013)	53 W	Ovarian	Intraperitoneal port placement	ST elevation	Non-obstructive CAD	Apical	15–20	NA	IABP, HIT, DIC, haemorrhagic stroke
Burgy *et al.*[32] (2014)	40 W	Breast	Lumpectomy	Sinus tachycardia	Normal coronary arteries	Mid-cavity	45	57 (NA)	NA
Joo *et al.*[33] (2011)	64 W	Liver tumour	Radio frequency ablation	ST elevation and Q wave	Normal coronary arteries	Apical	34	70	VT
Lee *et al.*[34] (2011)	51 M	Lung cancer	Lung resection	ST elevation	30% LAD	Apical	Severe dysfunction	Normal	Cardiac arrest and bradycardia
Guerrero *et al.*[35] (2009)	77 M	Oesophageal cancer	Bronchial stent		Normal sinus rhythm	Normal coronary arteries	15	55	Cardiogenic shock
Modi and Baig[36] (2009)	66 W	Breast	Radiation		T-wave inversion	Normal coronary arteries	NA	NA	NA
Schweizer *et al.*[37] (2011)	69 W	Laryngeal cancer	Clogged jejunostomy	ST elevation	Non-obstructive CAD	Apical	35–40	Normal	Hypotension
Singh *et al.*[38] (2014)	59 W	Lung	Pain crisis	ST elevation	Normal coronary arteries	Apical	35%	NA	NA

patient developed symptoms after 3 weeks of exposure to ibrutinib.[22] Alternatively, ibrutinib is a Btk inhibitor.[42] Bruton'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 phosphatidylinositol-4, 5-bisphosphate, a phosphatidylinositol, into two second messengers, inositol triphosphate (IP3) and diacylglycerol (DAG), which in turn activates protein kinase C.[43] Ibrutinib 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 symptoms of myocardial ischaemia and specific changes in electrocardiographic, echocardiographic, and cardiac angiographic examinations. Electrocardiogram commonly shows ST-segment elevation, followed by T-wave inversion in precordial leads; the cardiac enzymes are typically elevated; and echocardiography usually reveals hypokinesis, dyskinesis, 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 single 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 segment was involved, showing hyperkinesis of apical and basal ventricular 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 arrhythmias) have been reported.[48] The management of TC largely consists of supportive measures; the ventricular function usually recovers within 3–4 weeks.[49] Our patient had no pre-existing cardiovascular risk factors before starting ibrutinib; the only possible risk factor can be considered her age, given that TC is more common in post-menopausal women. The lack of any alternative explanation for our patient's clinical sign and symptoms supports our hypothesis that there is an association between the administration of ibrutinib and the development of TC. Because of the growing use of ibrutinib in diseases such as chronic lymphocytic leukaemia, mantle cell lymphoma, non-small-cell lung carcinoma, or autoimmune arthritis, our presumed association of ibrutinib and mid-cavitary TC deserves further prospective clinical observations.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from 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 committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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