ESC European Society of Cardiology

European Heart Journal - Case Reports (2019) **3**, 1–5
doi:10.1093/ehjcr/yty155

CASE REPORT
Heart failure

Omalizumab induced Takotsubo syndrome: case report

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Received 19 June 2018; accepted 23 November 2018; online publish-ahead-of-print 3 January 2019

Background Omalizumab is a humanized monoclonal anti-immunoglobulin E antibody, approved for the treatment of spontaneous chronic urticaria, with high efficacy and an excellent safety profile. Although its adverse effects are rare, allergic reactions and cardiovascular events were previously described.

Case summary The authors describe the case of a 75-year-old woman, followed at the outpatient dermatology clinic due to spontaneous chronic urticaria, treated with omalizumab 300 mg every 4 weeks. After the 11th administration of omalizumab, the patient developed an episode of thoracalgia associated with electro- and echocardiographic abnormalities. Coronary angiogram excluded coronary artery disease, and left ventriculography demonstrated mid-apical akinesia and basal hyperkinesia, consistent with the Takotsubo syndrome (TS).

Discussion Takotsubo syndrome was already reported in association with other monoclonal antibodies. However, to our knowledge, this is the first case of TS following the administration of omalizumab.

Keywords Takotsubo syndrome • Omalizumab • Case report • Left ventricular dysfunction

Learning points

- Omalizumab may be a cause of Takotsubo syndrome.
- It is of crucial importance to maintain adequate pharmacovigilance in order to detect adverse drug effects at an early stage.

Introduction

A Takotsubo syndrome (TS) is an acute, often reversible, dilated cardiomyopathy that clinically mimics an acute myocardial infarction and is usually associated with emotional or physical stress. There is considerable evidence that sympathetic stimulation is central to its pathogenesis, however, the precise pathophysiological mechanisms of TS are not completely understood.

There are rare cases described that associate TS with adverse drug reactions. This is the first known reported case of TS after administration of omalizumab.

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Handling Editor: Vijay Kunadian

Peer-reviewers: Domenico D'Amario and Rami Riziq Yousef Abumuaileq

Compliance Editor: Mark Philip Cassar

Supplementary Material Editor: Peysh A. Patel

Timeline

September 2016	Diagnosis of chronic urticaria resistant to oral antihistamines and initiation of medication with omalizumab
26 July 2017	Admitted to the hospital to have the 11th administration of omalizumab
	Thirty minutes later, the patient complained of oppressive chest pain
	Electrocardiogram showed alterations of repolarization
	Transthoracic echocardiogram showed mid-apical akinesia of the left ventricle with apical ballooning and reduced ejection fraction of 30%
	Coronary angiogram excluded atherosclerotic coronary disease
31 July 2017	Cardiac meta-iodobenzylguanidine (MIBG) scintigraphy showed decreased myocardial ^{123}I-MIBG uptake in the lateral, inferolateral, and apical walls
	All the investigations suggested Takotsubo syndrome
3 August 2017	Full recovery and discharge
August 2017	Cardiac MRI showed complete resolution
February 2018	Last follow-up. Patient in good clinical condition

Case presentation

A 75-year-old-woman with a history of Type 2 diabetes, hypertension, dyslipidaemia, and hypothyroidism was being followed up by the dermatology team for spontaneous chronic urticaria resistant to oral antihistamines, which was controlled with four weekly subcutaneous omalizumab 300 mg (Urticaria Activity Score Over 7 Days of 5).

Thirty minutes after the 11th administration of omalizumab, the patient complained of oppressive chest pain, lasting 30 min, without radiation, and no other associated symptomatology. On physical examination, she was hypertensive with blood pressure of 190/80 mmHg and heart rate of 70 b.p.m. Cardiac auscultation revealed presence of S1, S2, and S4 with no murmurs noted and lung auscultation was normal. The rest of the physical examination was unremarkable, namely with no other signs of heart failure, angioedema, or cutaneous lesions.

An electrocardiogram (EKG) was performed, showing a left anterior fascicular block *de novo*, besides the complete right bundle branch block already present. The 30-min EKG evolved with deep inversion of the V2–V6 T wave and loss of R waves in these leads (*Figure 1*). Laboratory tests showed troponin T values of 535 ng/dL (normal <14 ng/dL), creatine kinase-muscle/brain (CK-MB) of 248 U/L (normal <192 ng/dL), and C-reactive protein of 4.9 mg/dL (normal <0.5 mg/dL), without other significant changes.

A transthoracic echocardiogram was remarkable for akinesia of all the medial and apical segments of the left ventricle with apical ballooning, sparing the base of each wall, causing a reduced ejection fraction of 30%. The patient was administered loading doses of aspirin and clopidogrel and underwent coronary angiography, which excluded significant coronary artery disease. Ventriculography showed the existence of extensive mid-apical akinesia and basal hyperkinesia and confirmed the diagnosis of TS (*Figure 2*).

The patient was admitted to the cardiology ward for monitoring. Bisoprolol and ramipril were started at low dose and uptitrated.

The hospitalization was uneventful, with normalization of troponin, CK-MB levels, and inflammatory markers at Day 8. Repeat transthoracic echocardiography showed a global left ventricular ejection fraction of 56% at time of discharge. Serum and urinary catecholamines were not increased. Myocardial scintigraphy identified a decreased myocardial ^{123}I-meta-iodobenzylguanidine (MIBG) uptake in the lateral, inferolateral and apical walls, suggesting cardiac adrenergic nervous dysfunction (*Figure 3*). A low late heart-to-mediastinum ratio and a high washout rate were documented, a pattern usually observed in MIBG imaging in TS. The patient was discharged with bisoprolol 5 mg and ramipril 2.5 mg in addition to the previous medications. Omalizumab was discontinued.

The patient was evaluated 1 month after hospital discharge and the cardiac MRI performed at this time was normal (namely without alterations of the segmental contractility and a left ventricular ejection fraction of 66%), demonstrating the transient behaviour and complete resolution of this pathology.

Urticaria symptoms remained well controlled with oral antihistamines, after omalizumab withdrawal.

Discussion

Takotsubo syndrome is included in non-classified non-familial cardiomyopathies[1] and represents between 1.7% and 2.2% of patients with suspected acute coronary syndrome.[2] The pathophysiology of TS has not been fully elucidated, although the most accepted mechanism is a catecholaminergic excess,[3–5] which in turn causes microvascular dysfunction at the level of the coronary arteries causing vasospasm and transient decrease of blood flow to the myocardium, responsible for the dysfunction of ventricular segmental contractility. In fact, most reported cases are associated with sympathetic triggers such as the typical emotional or physical stress. However, there is increasing evidence that the pathophysiology of this disease may be more complex, involving direct myocardial injury.

In this case, and according to the new 2015 Heart failure Association of the European Society of Cardiology Takotsubo Syndrome Diagnostic criteria,[6] the diagnosis of TS was made based on the evidence of left ventricular mid and apical segments akinesis with apical ballooning; new electrocardiogram abnormalities; positive but relatively small elevation in cardiac troponins; absence of significant coronary artery disease or plaque rupture on angiograph; and recovery of ventricular systolic function on cardiac imaging at follow-up. An InterTAK Diagnostic Score[7] of 43 [female sex 25 points, absence of ST-segment depression (except in lead aVR) 12 points, and QTc prolongation 6 points] was suggestive of TS.

One may hypothesize about risk factors predisposing this patient to TS. In fact, TS most frequently affects older and post-menopausal women.[8] Women above the age of 55 seem to have a five-fold

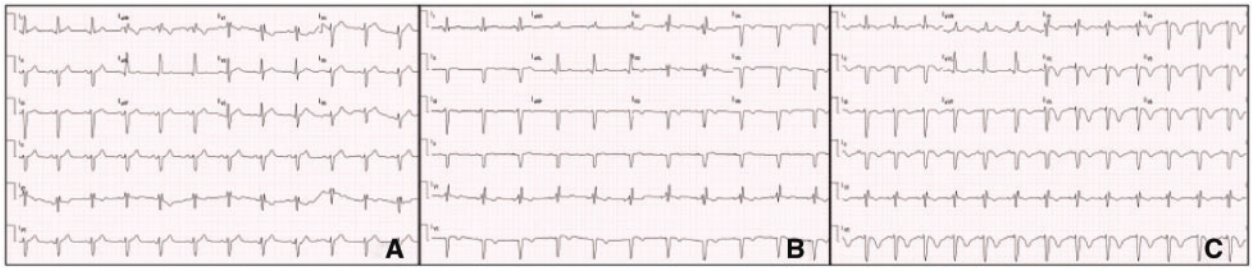

Figure 1 Electrocardiograms showing loss of R wave progression and T wave inversions in the anterior leads. EKG at presentation (*A*) showing a left anterior fascicular block de novo, besides the complete right bundle branch block already present. The 30-min EKG (*B*) evolving with inversion of V1-V6 wave and the 1 hour EKG showing deep T wave inversion and loss of R wave in all precordial leads (*C*).

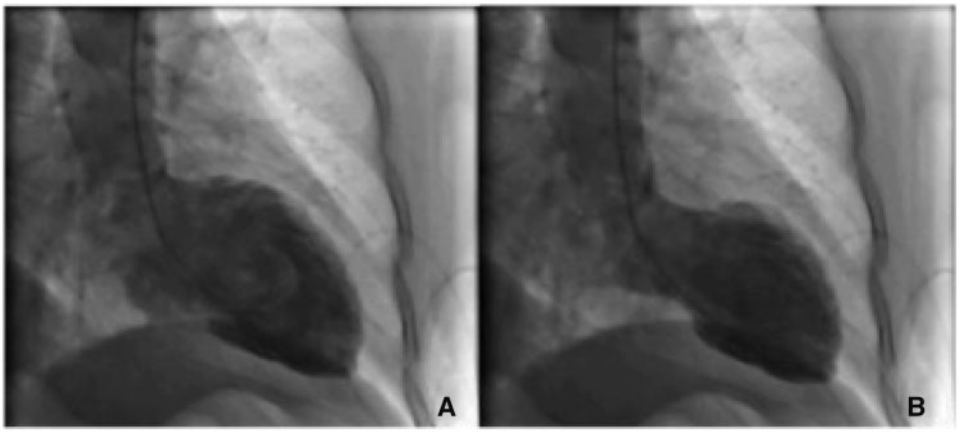

Figure 2 Left ventriculogram of patient in diastole (panel *A*) and systole (panel *B*) showing persistent mid-apical left ventricular akinesia with hyperkinesis of the remaining basal walls.

increased risk of developing TS than younger females.[9] Reduced oestrogen levels in menopausal women may render the heart more vulnerable to catechomaninergic stress, explaining the higher frequency of TS in this population.[10] Further studies are needed to better understand these associations.

After excluding the most frequent triggers, including previous history of emotional or physical stress, the administration of omalizumab appeared to be the main triggering factor of TS in this case. Indeed, TS has been increasingly associated with adverse drug events,[11] even though none so far has described the association with omalizumab.

Omalizumab is a monoclonal antibody that binds selectively to serum free immunoglobulin E, avoiding binding to its receptors and consequently inhibiting the inflammatory response induced by allergens, so is an effective drug in severe asthma and chronic spontaneous urticaria.[12]

Observational studies,[13] which included patients with moderate to severe asthma treated with omalizumab and a control group, showed that patients receiving this monoclonal antibody had a higher incidence at 5 years of cardiovascular events (acute myocardial infarction, unstable angina, transient ischaemic stroke, and cerebral thromboembolism), although cardiovascular death was similar in both groups. These adverse effects were not confirmed in subsequent studies.[14,15] Regarding these controversies, coupled with study limitations such as baseline discrepancies in asthma severity and cardiovascular risk factors between the two groups, as well as the elevated dropout rate, further evidence is needed to definitively confirm the cardiovascular risk and safety profile of omalizumab.

There are reported cases of TS secondary to the administration of several other monoclonal antibodies used in oncology such as rituximab,[16–18] bevacizumab,[19] transtuzumab,[20] and cetuximab.[21] The occurrence of TS was in these cases attributed more often to cardiotoxic direct effect, mostly via free radicals-induced cardiac myocyte damage and death.[17] However, other pathophysiological hypotheses were raised as a paraneoplastic phenomenon or stress associated with neoplasia.

A recent review examined 157[11] published cases of drug-dependent TS and showed that 68.2% of the cases were associated with excess catecholamines [either by exogenous administration (36.2%) or by drugs with a potential adrenergic effect (32%)], 8.9%

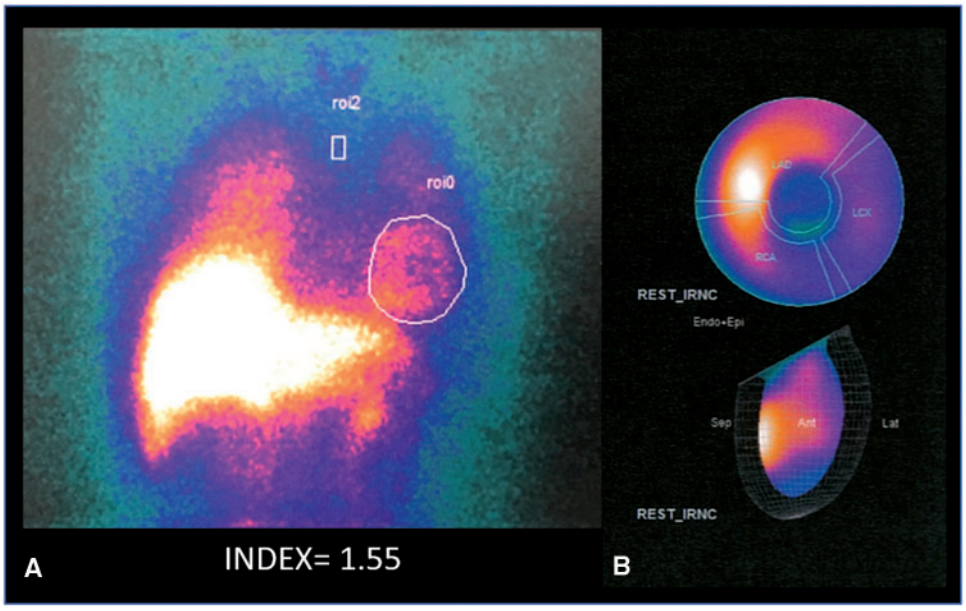

Figure 3 MIBG scintigraphy showing the heart/mediastinum ratio of 1.55 (*A*) and decreased myocardial ^{123}I-MIBG uptake in the lateral, inferolateral, and apical walls (*B*).

had a probable vasospastic aetiology, and in a significant percentage (20.4%) of the cases it was not possible to determine the most likely pathophysiological mechanism.

Although the pathophysiology of TS in the present case remains unconfirmed, we cannot exclude a possible role of a cardiotoxic effect of omalizumab in a predisposed patient with reduced oestrogen levels.

Even though it is rare, there are some reported cases of anaphylactic reactions following chronic administration of omalizumab. Price and Hamilton[22] have most likely hypothesized an anaphylactic reaction to an omalizumab excipient—polysorbate. Coors *et al.*[23] attempted to explain a case of anaphylaxis secondary to polysorbate and failed to demonstrate an immune response secondary to polysorbate but proved that this substance was capable of inducing mast cell degranulation.

Thus, in the present case, even though an anaphylactic reaction did not take place, the pathophysiological mechanism could be explained by a polysorbate-mediated mast cell degranulation with the release of mediators such as histamine, norepinephrine, epinephrine, which are inducers of coronary spasm.[24]

Besides that, it is not possible to exclude a cross-link omalizumab-specific IgG bound to macrophages through low-affinity receptor (FcRIII). The large antigen load afforded by the 300-mg injection may have been enough to cross-link omalizumab-specific IgG bound to macrophages through low-affinity FcRIII, causing the activation and degranulation of the mastocytes.

The fact that serum and urinary cathecolamine levels were normal may be due to the short half-life of these circulating hormones that can be degraded before evaluation of the hormones.

When applying the Naranjo scale[25] to our case, which assesses the likelihood of an adverse drug reaction, the causality between the administration of omalizumab and the development of TS is classified as possible (three points).

At a time when monoclonal antibodies have an increasing range of indications and are in exponential use, it is of crucial importance to maintain adequate pharmacovigilance in order to detect at an early stage potential adverse drug effects.

Conclusion

This is the first case described in the literature of TS after administration of omalizumab. As the aetiopathogenesis of TS is still under debate and the pathophysiology link with many drugs' side effects remain to be investigated, this case may provide valuable insights into the pathogenesis of TS. As our knowledge grows, the list of possible TS triggers may also grow. More TS reported cases and thorough registries are needed to better describe the triggers and to better understand this syndrome.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patients in line with COPE guidance.

Conflict of interest: none declared.

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