Transient global ventricular dysfunction in an adolescent affected by pancreatic adenocarcinoma

Maria Debora De Pasquale1*, Angela Mastronuzzi1, Luigi De Sio1, Annalisa Serra1, Chiara Grimaldi2, Marcello Chinali3 and Ugo Giordano3

Abstract

Background: Takotsubo cardiomyopathy (TC) is characterized by a transient decrease in ejection fraction and a reversible left ventricular dysfunction. The pathophysiology of TC is not completely understood. Heterogeneous and multifactorial mechanisms are involved: drugs, emotional and physical stress, genetic and hormonal factors.

Case presentation: A 17 year-old male with metastatic pancreatic adenocarcinoma, under chemotherapy containing 5-fluorouracil, presented severe left ventricular dysfunction requiring mechanical ventilation and inotropes administration. He completely recovered in 2 weeks.

Conclusion: To our knowledge this is the first report of transient form of ventricular dysfunction, mimicking TC, in an adolescent. We believe that children and adolescents receiving 5-fluorouracil should be closely monitored and referred for investigation if they develop cardiac symptoms.

Keywords: Takotsubo cardiomyopathy, Pediatrics, Pancreatic carcinoma, Reversible left ventricular dysfunction

Background

Takotsubo cardiomyopathy is a reversible cardiomyopathy characterized by a transient decrease in ejection fraction and a reversible left ventricular dysfunction. The pathophysiology of TC is not completely understood. Heterogeneous and multifactorial mechanisms are involved: drugs, emotional and physical stress, genetic and hormonal factors. TC is most often seen in elderly women and has never been reported in an adolescent [1].

Case Presentation

A 17 year-old male was diagnosed with metastatic pancreatic adenocarcinoma and started on chemotherapy with Oxaliplatin and Gemcitabine. He received the first two courses without any complications. The chemotherapy schedule was then modified to include FOLFIRINOX, on the basis of published data regarding the superiority of this drug combination compared to gemcitabine for the treatment of advanced pancreatic carcinoma [2]. He then received oxaliplatin, 85 mg/m², followed by leucovorin, 400 mg/ m², irinotecan, 180 mg/ m² and 5-fluorouracil (5-FU) at a dose of 400 mg/m² by intravenous bolus, followed by a continuous intravenous infusion of 2400 mg/m² over a 46-hour period. Approximately 4 h after the start of the first 5-FU infusion, the patient experienced vomiting and chest pain as well as an altered level of consciousness with extreme agitation. Progressive diuresis contraction was also recorded. Vital signs were: blood pressure 112/87 mmHg, heart rate 134/min and regular. Brain and thorax CT scans and abdominal x-ray were normal. Monitoring of vital signs revealed a progressive decrease of blood pressure down to 90/50 mmHg. Echocardiography showed severe and diffuse LV hypokinesis with an ejection fraction of 20 %. Moderate right ventricular hypokinesis and a 20 × 16 mm thrombus in the right atrium were also revealed (Additional file 1: Clip 1).

Plasma level of B-type natriuretic peptide was 800 pg/ml (normal value 0–100), while creatine kinase-MB, myoglobin and troponin levels were normal. Seventy-two hours...
later troponin and myoglobin levels rose to 0.16 ng/ml and 356 ng/ml respectively (normal values 0-0.10 and 0–170 respectively).

The patient was then transferred to the intensive care unit and placed on mechanical ventilation. Treatment with milrinone 0.75 mcg/kg/min, dopamine 12 mcg/kg/min, and epinephrine 0.05 mcg/kg/min was started together with anticoagulation based on heparin 20 UI/kg/h. Twenty-four hours later echocardiography showed no improvement in LV systolic and diastolic function. Levosimendan 0.1 mcg/kg/min and norepinephrine 0.06 mcg/kg/min were added while dosage of milrinone was decreased to 0.5 mcg/kg/min. Dobutamine and fenoldopam were also used. Vital signs improved slowly and echocardiography showed a progressive improvement in ventricular systolic and diastolic function (Additional file 2: Clip 2) with complete recovery after 14 days (Additional file 3: Clip 3). Under anticoagulation with low molecular weight heparin, the right atrial thrombus disappeared after 3 months. The final diagnosis was: reversible cardiomyopathy induced by 5-FU. Consequently, the chemotherapy schedule was modified and 5-FU administration excluded.

Discussion
We report a case of reversible cardiomyopathy induced by 5-FU. Takotsubo cardiomyopathy (TC), also known as apical ballooning syndrome, is a quite new clinical entity characterized by a transient decrease in ejection fraction and a reversible LV dysfunction consisting of dyskinesia involving the apical or midventricular segments. TC is most often seen in elderly women. In a review of studies from 2000 to 2012, Bossone et al reported that the age of patients affected by TC ranged from 59 to 73 years [1]. The pathophysiology of TC has not been fully identified. Heterogeneous and multifactorial mechanisms are involved [3–7]. Emotional and physical stress may play a role by releasing circulating catecholamines that have direct effects on the myocardium. The mechanism underlying the association between sympathetic stimulation and myocardial stunning is unknown. One possibility is ischemia resulting from epicardial coronary arterial spasm. An alternative mechanism is microvascular spasm. Abnormal coronary flow in the absence of obstructive disease has been reported in patients with stress-related myocardial dysfunction. A third possible mechanism of catecholamine-mediated myocardial stunning is direct myocyte injury, through cyclic AMP–mediated calcium overload or by producing oxygen-derived free radicals [4]. Familial cases of TC are also described, suggesting a genetic role in the pathogenesis of this condition [5]. However, estrogen deficiency may also be a risk factor in the development of this type of reversible cardiomyopathy. This deficiency could explain the high incidence in postmenopausal women [6].

Several reports have discussed drugs that may cause TC [3, 7]. Among these, 5-FU is described as a potential cause. Cardiotoxicity is a well-known adverse effect of 5-FU which occurs in 1.2 to 18 % of patients, but the mechanism involved is still not fully understood [8, 9]. In recent years several cases of 5-FU-induced Takotsubo-like syndrome have been reported in the literature [10–12]. It has been hypothesized that extreme sympathetic stimulation causing coronary vasospasm may play a role in the development of TC.

According to the reported cases, TC is often seen in elderly women who frequently have histories of smoking, alcohol abuse, anxiety states, and hyperlipidemia. Our patient however, was an adolescent, with no previous history of cardiac dysfunction or other reported risk factors. He was under treatment for pancreatic adenocarcinoma with liver metastases and, 4 h after the start of 5-FU infusion, he developed chest pain and an altered level of consciousness, which are typical findings associated with TC. Echocardiography showed severe and diffuse LV hypokinesis with an increased level of cardiac enzyme B-Type natriuretic peptide, troponin and myoglobin, leading us to hypothesize TC. To our knowledge this is the first reported case of 5-FU- induced transient form of ventricular dysfunction, mimicking TC, in an adolescent. This is probably due to the fact that the drugs recognized as possible triggers of TC are not currently used in pediatric and young populations affected by cancer [3].

The chemotherapeutic agent 5-FU, by inhibiting thymidylate synthase in malignant cells, disrupts DNA synthesis and promotes cell death. It is currently used as adjuvant chemotherapy for colorectal cancer and frequently for the treatment of pancreatic, breast, bladder, gastric, esophageal and prostate cancer [8]. These neoplasms rarely affect adolescents. In the USA, the annual age-adjusted incidence rate for all carcinomas in patients younger than 20 years is 1.4 per million. More specific figures for pancreatic cancers in this age group are unavailable [13]. The only occasional use of 5-FU in the pediatric population could explain the absence of reports of TC in this age group. This is in fact the first observation of Takotsubo-like syndrome, in an adolescent.

Conclusion
Although TC has only been reported in adults, children and adolescents with cardiac symptoms during chemotherapy with 5-fluorouracil should be closely monitored and referred for further investigations if there is suspicion of this condition. Prompt acute
clinical assessment coupled with ECG recordings and cardiac enzyme analysis should be performed if cardiotoxicity is suspected. Further studies are necessary to be able to assess the real incidence of TC in the pediatric population.

Additional files

Additional file 1: Clip 1. Exam performed on May 17th. Diffuse left ventricular hypokinesia can be observed with apical dyskinesia and dilation. (AVI 17411 kb)

Additional file 2: Clip 2. Exam performed on May 23rd. Improvement in left ventricular function is observed, with mild diffuse hypokinesia and normal left ventricular geometry. (AVI 6992 kb)

Additional file 3: Clip 3. Exam performed after 6 months. Normal left ventricular geometry and function is restored. (MPEG 1612 kb)

Abbreviations

5-FU, 5-fluoruracil; LV, left ventricular; TC, takotsubo cardiomyopathy

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Availability of data and materials

All the data are contained within the manuscript.

Authors’ contributions

MDDP was responsible for literature review, conception and preparation of the manuscript. AM drafted the manuscript. LDS, AS and UG participated in preparation and critical revision of the manuscript. CG performed surgery on the patient and participated in preparation and critical revision of the manuscript. MC carried out all cardiac scans on the patient, selecting the videos for the manuscript, and participated in preparation and critical revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Written informed consent was obtained from the patient’s parents for publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Ethics approval and consent to participate

Approval of IRB was not necessary for this paper since it is a case-report.

Author details

1Department of Pediatric Hematology/Oncology and Stem Cell Transplantation, Bambino Gesù Children’s Hospital, Piazza Sant’Onofrio, 4, 00165 Rome, Italy. 2Pediatric Surgery and Transplantation, Rome, Italy. 3Pediatric Cardiology, Bambino Gesù Children’s Hospital, Rome, Italy.

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References

1. Bossone E, Savarese G, Ferrara F, et al. Takotsubo cardiomyopathy, an overview. Heart Fail Clin. 2013;9:246–66.
2. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–25.
3. Izumi I. Drug-induced Takotsubo cardiomyopathy. Heart Fail Clin. 2013;9:225–31.
4. Wittstein IS, Thieman DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352:539–48.
5. Cherian J, Angelis D, Filiberti A, et al. Can takotsubo cardiomyopathy be familial? Int J Cardiol. 2007;121:74–5.
6. Ueyama T, Kasamatsu K, Hano T, et al. Catecholamines and estrogen are involved in the pathogenesis of emotional stress-induced acute heart attack. Ann N Y Acad Sci. 2000;914:479–85.
7. Amariles P. A comprehensive literature search: drugs as possible triggers of takotsubo cardiomyopathy. Curr Clin Pharmacol. 2011;6(1):1–11.
8. Jensen SA, Sorensen JB. 5-Fluorouracil-based therapy induces endovascular injury having potential significance to development of clinically overt cardiotoxicity. Cancer Chemother Pharmacol. 2012;69:57–64.
9. Stewart T, Pavlakis N, Ward M. Cardiotoxicity with 5-fluorouracil and capecitabine: more than just vasospastic angina. Intern Med J. 2010;40:303–7.
10. Gianni M, Dentali F, Lonn E. 5 fluorouracil-induced apical ballooning syndrome: a case report. Blood Coagul Fibrinolysis. 2009;20:306–8.
11. Basselin C, Fontangens T, Descotes J, et al. 5-fluorouracil-induced Tako-Tsubo-like syndrome. Pharmacotherapy. 2011;31:226.
12. Ozturk MA, Ozveren O, Cinar V, et al. Takotsubo syndrome: an underdiagnosed complication of 5-fluorouracil mimicking acute myocardial infarction. Blood Coagul Fibrinolysis. 2013;24(1):90–4.
13. Pizzo PA, Poplack DG. Principles and practice of pediatric oncology. Fourth edition, Philadelphia: Lippincott Williams & Wilkins.