

Rapid, Fatal Acute Right Ventricular Failure

After Locoregional Cytokine Therapy
for Uveal Melanoma Liver Metastases

Rajiv A. Kabadi, MD, MS
Mital Shah, MD
Gregary D. Marhefka, MD
Gautam George, MD
Bharat Awsare, MD
Mizue Terai, PhD
Takami Sato, MD, PhD

Locoregional cytokine treatment, or immunoembolization, is an experimental targeted therapy for uveal melanoma metastatic to the liver. Unlike systemic cytokine treatments that have been associated with substantial toxicity, this method of drug delivery appears to be better tolerated. Because this newer therapy is being prescribed more widely, oncologists, interventional radiologists, cardiologists, pulmonologists, critical care specialists, and other providers should become familiar with potential adverse reactions.

We describe the case of a 67-year-old man who had metastatic uveal melanoma. Before he underwent liver-directed immunoembolization, he had elevated markers of endothelial dysfunction. He died after the rapid onset of acute right ventricular failure from severe pulmonary hypertension with possible superimposed isolated right ventricular takotsubo cardiomyopathy. In discussing this rare case, we focus on the differential diagnosis. (Tex Heart Inst J 2020;47(3):224-8)

Key words: Acute disease; biomarkers, tumor; cytokines/immunology; disease progression; fatal outcome; inflammation mediators/metabolism; myocardial infarction/physiopathology; neoplasm metastasis; takotsubo cardiomyopathy/etiology; ventricular dysfunction, right/physiopathology

From: Department of Medicine (Drs. Kabadi and Shah); Department of Medicine, Divisions of Cardiology (Dr. Marhefka) and Pulmonary and Critical Care Medicine (Drs. Asware and George); and Department of Medical Oncology (Drs. Sato and Terai); Thomas Jefferson University Hospital, Philadelphia, Pennsylvania 19107

Address for reprints:
Rajiv A. Kabadi, MD,
2 Oxford Dr.,
Montville, NJ 07045

E-mail: Rajiv.a.kabadi@gmail.com

© 2020 by the Texas Heart[®]
Institute, Houston

For more than a decade, immunomodulatory pharmacologic therapies that augment cancer-specific immune responses have been used to treat malignant melanoma.¹ It has become apparent that cutaneous and uveal forms of melanoma respond differently to similar treatments—uveal melanoma (UM), often poorly. This has hindered the development of standard care for treating UM and has prompted investigation of various experimental therapies.²

Systemic treatment with cytokines has been associated with substantial toxicities involving systemic inflammatory response syndromes. Conversely, results of preliminary studies suggest that locoregional cytokine treatment, also called immunoembolization (IE), is better tolerated and remains therapeutically beneficial during treatment of UM metastatic to the liver.³

We present a rare, fatal case of isolated right ventricular (RV) failure from acute severe pulmonary hypertension with possible superimposed isolated RV takotsubo cardiomyopathy (TC) in a patient whose metastatic UM we treated with liver-directed IE.

Case Report

In March 2017, a 67-year-old man with hypertension, type 2 diabetes, obstructive sleep apnea, coronary artery disease, stage 2 chronic kidney disease, and metastatic UM was electively admitted to undergo catheter-directed local cytokine-based IE for liver metastases. He had been diagnosed with UM approximately one year earlier and had undergone plaque brachytherapy with adjuvant valproic acid in a clinical trial. He was removed from the trial after new liver lesions were confirmed as metastatic disease. An echocardiogram 6 months before his current presentation showed normal left ventricular (LV) systolic function, mild LV diastolic dysfunction, normal RV size and function, and a normal estimated pulmonary artery (PA) pressure.

On admission, the patient reported only chronic lower back pain. He was alert and oriented, with normal vital signs. Laboratory results were notable only for stable chronic kidney disease (creatinine, 1.2 mg/dL). We measured his serum levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) with use of an enzyme-linked immunosorbent assay kit (R&D Systems, a Bio-Techne brand), and analyzed his serum cytokine and chemokine levels by using a bead-based Multiplex[®] assay with Luminex[®] technology (Millipore Sigma).

The next morning, we entered his right hepatic artery with use of a transfemoral

microcatheter. We injected 1,500 µg of GM-CSF and 2,000,000 IU of interleukin (IL)-2 suspended in 5 mL of ethiodized oil, then used interventional radiology and IE to embolize the hepatic artery with gelatin sponge particles. No procedural complications occurred, and the patient was returned to his room for overnight observation.

Approximately 11 hours after IE, the patient experienced mild hypoxemia (pulse oximetry saturation, 88%) that improved when 2 L/min of supplemental oxygen was supplied through a nasal cannula. A chest radiograph showed linear atelectasis of his right lower lobe. During the next several hours, he became febrile (100.6 °F), tachycardic (106 beats/min), tachypneic (24 breaths/min), and progressively hypoxemic (pulse oximetry saturation, 94% on 6 L/min of oxygen via nasal cannula).

Laboratory results included leukopenia (white blood cell count, $1.3 \times 10^9/L$; 36% lymphocytes), elevated liver enzyme levels with a hepatocellular injury pattern (total bilirubin, 1.3 mg/dL; alkaline phosphatase, 369 IU/L; aspartate aminotransferase [AST], 2,049 IU/L; and alanine aminotransferase [ALT], 1,647 IU/L), lactic acidosis (lactate, 6.5 mmol/L), an elevated cardiac troponin T level (0.08 ng/mL), an elevated N-terminal-pro-B-type natriuretic peptide level (3,711 pg/mL), and acute kidney injury (creatinine, 1.8 mg/dL). An electrocardiogram (ECG) showed sinus tachycardia with normal intervals and no ischemic changes. Ventilation-perfusion scintigraphy results were negative for segmental perfusion defects. Chest computed tomograms without contrast revealed scattered parenchymal nodules, mild interstitial edema, mild PA dilation, and, as expected, persistent embolic material within the liver. The patient's respiratory status rapidly declined during the next several hours despite aggressive intravenous diuretic and broad-spectrum antibiotic therapy. He was started on noninvasive positive-pressure ventilation and was transferred to intensive care during the morning of hospital day 3, approximately 24 hours after IE.

The patient became disoriented to time and place. An echocardiogram obtained during positive-pressure ventilation showed a mildly dilated RV with hyperdynamic apical motion associated with hypokinesis of remaining segments (the McConnell sign), mild-to-moderate tricuspid insufficiency, severe pulmonary hypertension (estimated right atrial pressure, 10 mmHg; estimated PA systolic pressure, 73 mmHg), and a hyperdynamic LV without segmental wall-motion abnormalities (Fig. 1A). Concerned about possible capillary leak syndrome (CLS), we administered 8 mg of intravenous dexamethasone. Despite all interventions, the patient's respiratory and mental status continued to decline, and he needed endotracheal intubation and ventilator placement approximately 36 hours after IE.

Overnight on hospital day 3, the patient's rapidly progressive hemodynamic instability necessitated multiple sequential vasopressor infusions. Serial bloodwork

results included increasing transaminase levels (AST, 2,944 IU/L; ALT, 2,364 IU/L), coagulopathy (international normalized ratio, 2.14), and increased cardiac troponin T (peak level, 1.37 ng/mL). An ECG then showed sinus tachycardia with 1-mm ST-segment elevations in leads II, aVR, V₁, and V₂, and 2-mm ST-segment depressions in leads I, II, aVL, V₅, and V₆. An echocardiogram showed the McConnell sign with an underfilled and persistently hyperdynamic LV. We initiated epoprostenol inhalation therapy for acute pulmonary hypertension and acute RV failure (cor pulmonale).

Echocardiograms obtained during the morning of hospital day 4 indicated progressive RV enlargement and severe global RV dysfunction, RV apical dysfunction, and a smaller, underfilled LV (Fig. 1B–C). A right-sided ECG revealed sinus tachycardia with 1- to 1.5-mm ST-segment elevation in leads V_{3R} and V_{4R}, suggesting acute RV myocardial infarction (MI) (Fig. 2). Emergency cardiac catheterization was not possible because of the patient's progressive hemodynamic instability. Systemic thrombolytic therapy was considered; however, the patient had a cardiac arrest with pulseless electrical activity, and he died.

Autopsy findings included mild-to-moderate coronary artery atherosclerosis without substantial stenosis, mild bilateral pulmonary edema, and multiple liver metastases from primary UM. There was no evidence of acute MI, acute pulmonary embolism (PE), or acute myocarditis. No obvious cause of death was identified.

In search of answers, we reexamined our patient's laboratory results. Before IE, his transforming growth factor β1 (TGF-β1) concentration had been 12,931 pg/mL, much higher than the mean reference level of $3,111 \pm 2,464$ pg/mL in 23 previous patients with UM before liver-directed IE (unpublished data). Our patient's baseline levels of IL-6 (<0.9 pg/mL), IL-8 (7.7 pg/mL), tumor necrosis factor-α (TNF-α) (7.68 pg/mL), and GM-CSF (<3 pg/mL) were similar to those of the previous patients. However, on posttreatment day 1, his IL-6 and IL-8 concentrations were 673.3 and 2,093 pg/mL, respectively; on day 2, they decreased to 448.8 and 692.2 pg/mL. On those same days, his TNF-α levels (54.9 and 8.2 pg/mL) and GM-CSF levels (11.5 and 8.9 pg/mL) did not differ greatly from those in the other patients who had undergone liver-directed IE. We considered these factors in the differential diagnosis.

Discussion

The autopsy findings in our patient excluded typical causes of death, such as MI and PE. One diagnosis that could have been missed, however, is pulmonary ethiodized oil embolism. This rare complication can occur when a systemic shunt enables cardiopulmonary transit of the oil. We had not considered this phenomenon in the differential diagnosis of our patient because it has

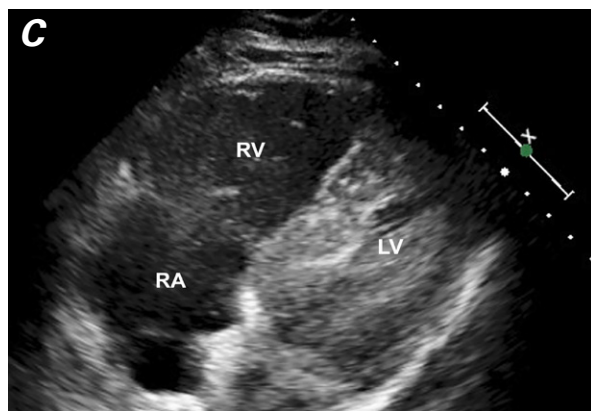
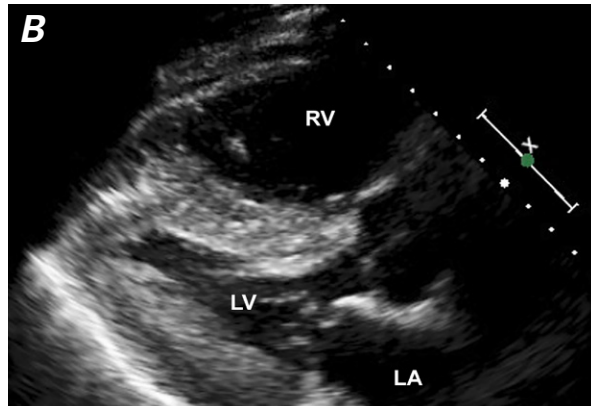
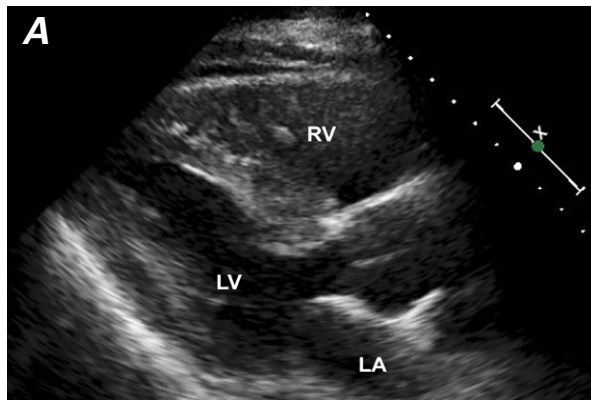


Fig. 1 End-diastolic transthoracic echocardiograms. Parasternal long-axis views show **A**) mild right ventricular (RV) enlargement and a hyperdynamic left ventricle (LV) of relatively normal size on hospital day 3, and **B**) progressive RV enlargement and reduced LV size from interventricular septal shift and reduced LV filling on day 4. **C**) The end-diastolic apical 4-chamber view shows substantial RV enlargement and reduced LV size with hyperdynamic RV apical motion associated with hypokinesis of remaining segments (the McConnell sign).

LA = left atrium; RA = right atrium

not been associated with as little as 5 mL of oil. The oil's high radiopacity enabled us to rule out this diagnosis because the patient's chest computed tomograms were negative for PE, and the oil deposit's intrahepatic appearance was stable well after respiratory failure began. Finally, postmortem histopathologic examination pro-

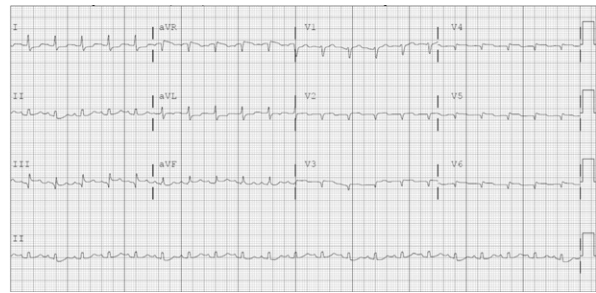


Fig. 2 Right-sided electrocardiogram immediately before cardiac arrest shows sinus tachycardia and 1- to 1.5-mm ST-segment elevations in leads V_3R and V_4R , suggesting acute right ventricular myocardial infarction.

duced no findings consistent with previous descriptions of alveolar hemorrhagic edema with fat droplet deposition and fibrin thrombi.⁴

Our differential diagnosis also included CLS, the most prevalent severe toxicity in patients who undergo systemic high-dose IL-2 therapy. It presents much like septic shock, with tachycardia, tachypnea, respiratory failure, and hypotension caused by acute endothelial dysfunction, capillary hyperpermeability, and rapid efflux of serum and plasma proteins from the intravascular compartment.⁵⁻⁷ Although our patient probably had endothelial dysfunction, we think that CLS was not the primary process driving his clinical deterioration, because antemortem images, laboratory results, and clinical and postmortem evaluations revealed no notable fluid or protein extravasation. Moreover, systemic CLS has not been reported after local therapy with low-dose IL-2.

The McConnell sign, described as severe RV hypokinesis with apical sparing, is seen in but is not specific to acute PE.⁸ Right ventricular failure due to acute right-sided heart strain secondary to acute, severe pulmonary hypertension, estimated by our patient's initial echocardiogram, may have produced the McConnell sign in our patient, even though he had no signs of acute PE at autopsy. His acute pulmonary hypertension may have been related to GM-CSF-induced neutrophil activation and adhesion to the pulmonary vasculature endothelium, which would also explain his paradoxical leukopenia.⁹⁻¹¹ The lack of prominent findings on chest images and the absence of PA thrombi at autopsy, however, make this unlikely. His leukopenia also may have resulted from granulocyte activation and adhesion within the hepatic vasculature due to uniquely high sensitivity to GM-CSF, which would explain his severely elevated transaminase levels consistent with hepatitis.

Acute RV myocardial infarction can also mimic the McConnell sign. However, the autopsy findings ruled this out despite the ST-segment elevation in the right-sided precordial leads with progressive RV dysfunction and apical involvement.

Acute myocarditis as an adverse reaction to high-dose IL-2 therapy can be diffuse or localized.¹² However, our patient was given low-dose IL-2, and the autopsy findings excluded acute myocardial inflammation.

Last, pathologic states associated with exaggerated sympathetic stimulation, such as sepsis, are recognized precipitants of myocardial depression and TC.^{13,14} Because the proinflammatory effects of cytokines *in vivo* have been clarified,¹⁵ mounting evidence suggests that consequent myocardial inflammation plays a key role in the pathogenesis of TC.¹⁶⁻¹⁹ Without indications of acute MI, PE, or myocarditis at autopsy, and given the isolated right-sided ST-segment elevation, our patient may have had a rare, isolated right ventricular TC superimposed on the acute cor pulmonale—a condition reported only 8 times.²⁰⁻²⁷ His progressive RV dilation without apical sparing makes this a diagnosis of exclusion and difficult to prove, but nevertheless a possible explanation for his profound, rapid, ultimately fatal deterioration.

The Inflammatory Response and Interpretation of the Cytokine Data

Interleukin-6 and IL-8, key inflammatory mediators, become elevated in the plasma of patients with heart failure proportional to disease severity, and they can independently predict death.²⁸⁻³⁰ Serum levels of IL-6 have specifically been associated with major coronary events, cardiovascular and all-cause death, MI, and cancer death in patients with stable coronary heart disease.³¹ Moreover, in patients with TC, high IL-6 levels on admission have been associated with higher rates of adverse events during follow-up.³² Despite this supporting evidence, attempts to use IL-6 to predict adverse cardiovascular outcomes have failed to improve risk stratification.³³ Our patient had normal baseline IL-6 and IL-8 levels, so their increase in the absence of MI may have indicated severe isolated RV failure.

Serum concentrations of TGF- β 1 in patients with sepsis quantify the severity of endothelial dysfunction and predict their risk of developing severe vascular inflammatory disease.³⁴ Our patient's baseline TGF- β 1 level was markedly higher than that in other patients with metastatic UM, suggesting that existing endothelial dysfunction predisposed him to acute severe pulmonary hypertension and RV failure.

Investigators in several large cohort studies have reported more malignancies in patients with TC than in the general population, leading to the conjecture that TC is a paraneoplastic phenomenon.³⁵ Reciprocal interactions between tumor cells and vascular endothelial cells may induce endothelial dysfunction, evidenced in our patient by an elevation in TGF- β 1 concentration, which has been observed in patients with active malignancies.^{36,37} That our patient had such progressive RV failure, seemingly out of proportion to severe pulmonary hypertension alone, suggests that malignant

cell-induced endothelial dysfunction contributed to a superimposed TC state that ultimately led to death.

Conclusions

This case of acute, severe pulmonary hypertension and acute RV failure (cor pulmonale) developed within 24 hours of intrahepatic GM-CSF and IL-2 therapy for metastatic UM.

The isolated and progressive acute RV dilation and dysfunction seen on echocardiograms—out of proportion to acute pulmonary hypertension alone, with isolated ST-segment elevation in the right-sided leads and no acute MI, PE, or myocarditis—also suggest a superimposed isolated right ventricular TC. This may have resulted from a catecholamine surge consequent to treatment-related CLS in the presence of existing endothelial dysfunction suggested by the elevated inflammatory markers IL-6, IL-8, and TGF- β 1. Oncologists, interventional radiologists, cardiologists, pulmonologists, critical care specialists, and other providers should be aware of this potential adverse reaction. Future studies are needed to clarify the relationship between serum markers of endothelial dysfunction and the development of severe, acute pulmonary hypertension and possible superimposed TC in patients with liver-metastatic melanoma who have undergone intrahepatic GM-CSF and IL-2 therapy.

Acknowledgments

We acknowledge all the healthcare providers who contributed to our patient's care, including Carin Gonsalves, MD; Aileen Deng, MD; Amy Javia, MD; Frances Mae West, MD; and John Farber, MD.

References

1. Orloff M, Valsecchi ME, Sato T. Successes and setbacks of early investigational drugs for melanoma. *Expert Opin Investig Drugs* 2015;24(8):993-7.
2. Terai M, Mastrangelo MJ, Sato T. Immunological aspect of the liver and metastatic uveal melanoma. *J Cancer Metastasis Treat* 2017;3(10):231-43.
3. Valsecchi ME, Terai M, Eschelmann DJ, Gonsalves CF, Chervoneva I, Shields JA, et al. Double-blinded, randomized phase II study using embolization with or without granulocyte-macrophage colony-stimulating factor in uveal melanoma with hepatic metastases. *J Vasc Interv Radiol* 2015;26(4):523-32.e2.
4. Hatamaru K, Azuma S, Akamatsu T, Seta T, Urai S, Uenoyama Y, et al. Pulmonary embolism after arterial chemoembolization for hepatocellular carcinoma: an autopsy case report. *World J Gastroenterol* 2015;21(4):1344-8.
5. Alwan LM, Grossmann K, Sageser D, Van Atta J, Agarwal N, Gilreath JA. Comparison of acute toxicity and mortality after two different dosing regimens of high-dose interleukin-2 for patients with metastatic melanoma. *Target Oncol* 2014;9(1):63-71.

6. White RL Jr, Schwartzentruber DJ, Guleria A, MacFarlane MP, White DE, Tucker E, Rosenberg SA. Cardiopulmonary toxicity of treatment with high dose interleukin-2 in 199 consecutive patients with metastatic melanoma or renal cell carcinoma. *Cancer* 1994;74(12):3212-22.
7. Pineton de Chambrun M, Luyt CE, Beloncle F, Gousseff M, Mauhin W, Argaud L, et al. The clinical picture of severe systemic capillary-leak syndrome episodes requiring ICU admission. *Crit Care Med* 2017;45(7):1216-23.
8. Vaid U, Singer E, Marhefka GD, Kraft WK, Baram M. Poor positive predictive value of McConnell's sign on transthoracic echocardiography for the diagnosis of acute pulmonary embolism. *Hosp Pract* 2013;41(3):23-7.
9. Yong KL, Rowles PM, Patterson KG, Linch DC. Granulocyte-macrophage colony-stimulating factor induces neutrophil adhesion to pulmonary vascular endothelium in vivo: role of beta 2 integrins. *Blood* 1992;80(6):1565-75.
10. Singh NRP, Johnson A, Peters AM, Babar J, Chilvers ER, Summers C. Acute lung injury results from failure of neutrophil de-priming: a new hypothesis. *Eur J Clin Invest* 2012;42(12):1342-9.
11. Hellmich B, Csernok E, Trabandt A, Gross WL, Ernst M. Granulocyte-macrophage colony-stimulating factor (GM-CSF) but not granulocyte colony-stimulating factor (G-CSF) induces plasma membrane expression of proteinase 3 (PR3) on neutrophils in vitro. *Clin Exp Immunol* 2000;120(2):392-8.
12. Tan MCC, Ortega-Legaspi JM, Cheng SF, Patton KK. Acute myocarditis following high-dose interleukin-2 treatment. *J Cardiol Cases* 2016;15(1):28-31.
13. Y-Hassan S, Settergren M, Henareh L. Sepsis-induced myocardial depression and takotsubo syndrome. *Acute Card Care* 2014;16(3):102-9.
14. Wittstein IS, Thiemann DR, Lima JAC, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;352(6):539-48.
15. Andreis DT, Singer M. Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. *Intensive Care Med* 2016;42(9):1387-97.
16. Morel O, Sauer F, Imperiale A, Cimarelli S, Blondet C, Jesel L, et al. Importance of inflammation and neurohumoral activation in takotsubo cardiomyopathy. *J Card Fail* 2009;15(3):206-13.
17. Kawai S, Shimada T. Inflammation in takotsubo cardiomyopathy? Inquiry from "Guidelines for Diagnosis and Treatment of Myocarditis (JCS 2009)". *J Cardiol* 2014;63(4):247-9.
18. Khalid N, Ahmad SA, Umer A, Chhabra L. Takotsubo cardiomyopathy and myopericarditis: unraveling the inflammatory hypothesis. *Int J Cardiol* 2015;196:168-9.
19. Y-Hassan S. Myocarditis and takotsubo syndrome: are they mutually exclusive? *Int J Cardiol* 2014;177(1):149-51.
20. Elikowski W, Malek-Elikowska M, Rozanska P, Fertala N, Zawodna M. Isolated right ventricular takotsubo cardiomyopathy: a case report and literature review. *Pol Merkur Lekarski* 2016;41(246):283-6.
21. Mrdovic I, Kostic J, Perunicic J, Asanin M, Vasiljevic Z, Ostojic M. Right ventricular takotsubo cardiomyopathy. *J Am Coll Cardiol* 2010;55(16):1751.
22. Burgdorf C, Hunold P, Radke PW, Schunkert H, Kurowski V. Isolated right ventricular stress-induced (Tako-Tsubo) cardiomyopathy. *Clin Res Cardiol* 2011;100(7):617-9.
23. Stähli BE, Ruschitzka F, Enseleit F. Isolated right ventricular ballooning syndrome: a new variant of transient cardiomyopathy. *Eur Heart J* 2011;32(14):1821.
24. Joe BH, Hwang HJ, Park CB, Jin ES, Sohn IS, Cho JM, Kim CJ. Takotsubo cardiomyopathy recurrence with left ventricular apical ballooning following isolated right ventricular involvement: a case report. *Exp Ther Med* 2013;6(1):260-2.
25. Chandorkar A, Codolosa JN, Lippmann ML, Pressman GS, Sta Cruz JP. Recurrent right ventricular takotsubo cardiomyopathy in a patient with recurrent aspiration. *Echocardiography* 2014;31(8):E240-2.
26. Kagiya N, Okura H, Kume T, Hayashida A, Yoshida K. Isolated right ventricular takotsubo cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2015;16(3):285.
27. Maeba H, Senoh T, Suwa Y, Miyasaka Y, Shiojima I. P24-4 - Cardiac arrest caused by isolated right ventricular takotsubo cardiomyopathy [abstract]. *J Card Fail* 2017;23(10 Suppl):S84.
28. Tsutamoto T, Hisanaga T, Wada A, Maeda K, Ohnishi M, Fukai D, et al. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. *J Am Coll Cardiol* 1998;31(2):391-8.
29. Nymo SH, Hulthe J, Ueland T, McMurray J, Wikstrand J, Askevold ET, et al. Inflammatory cytokines in chronic heart failure: interleukin-8 is associated with adverse outcome. Results from CORONA. *Eur J Heart Fail* 2014;16(1):68-75.
30. Hogue M, Mandi Y, Csanady M, Sepp R, Buzas K. Comparison of circulating levels of interleukin-6 and tumor necrosis factor-alpha in hypertrophic cardiomyopathy and in idiopathic dilated cardiomyopathy. *Am J Cardiol* 2004;94(2):249-51.
31. Held C, White HD, Stewart RAH, Budaj A, Cannon CP, Hochman JS, et al. Inflammatory biomarkers interleukin 6 and C reactive protein and outcomes in stable coronary heart disease: experiences from the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) Trial. *J Am Heart Assoc* 2017;6(10):e005077.
32. Santoro F, Tarantino N, Ferraretti A, Ieva R, Musaico F, Guastafierro F, et al. Serum interleukin 6 and 10 levels in takotsubo cardiomyopathy: increased admission levels may predict adverse events at follow-up. *Atherosclerosis* 2016;254:28-34.
33. Nymo SH, Aukrust P, Kjekshus J, McMurray JJV, Cleland JGF, Wikstrand J, et al. Limited added value of circulating inflammatory biomarkers in chronic heart failure. *JACC Heart Fail* 2017;5(4):256-64.
34. Bae JS, Lee W, Nam JO, Kim JE, Kim SW, Kim IS. Transforming growth factor-β induced protein promotes severe vascular inflammatory responses. *Am J Respir Crit Care Med* 2014;189(7):779-86.
35. Burgdorf C, Kurowski V, Bonnemeier H, Schunkert H, Radke PW. Long-term prognosis of the transient left ventricular dysfunction syndrome (Tako-Tsubo cardiomyopathy): focus on malignancies. *Eur J Heart Fail* 2008;10(10):1015-9.
36. Nikitenko LL. Vascular endothelium in cancer. *Cell Tissue Res* 2009;335(1):223-40.
37. Lippitz BE. Cytokine patterns in patients with cancer: a systematic review. *Lancet Oncol* 2013;14(6):e218-28.