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Case Report / Приказ болесника

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Right-sided heart failure as a first presentation of portopulmonary hypertension

Инсуфицијенција десног срца као прва манифестација портопулмоналне хипертензије

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Right-sided heart failure as a first presentation of portopulmonary hypertension

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SUMMARY

Introduction Pulmonary artery hypertension and right ventricular failure are potentially fatal complications that can develop in patients with portal hypertension. The objective of this case report was to report a patient with end stage liver disease, and portal and pulmonary artery hypertension and right heart failure.

Case outline A 57-year-old man was admitted to the Cardiology Department of tertiary hospital due to signs of right sided heart failure, ascites, pleural effusions, and pretibial edema. The patient had the history of alcohol abuse, arterial hypertension and gout. Just prior to the admission, abdominal ultrasound revealed granular liver structure, as well as ascites. Laboratory tests showed microcytic anemia, values of transaminases below referent, hypoalbuminemia, low creatinine clearance. Echocardiography revealed pulmonary hypertension (PH) and right ventricle failure. Right heart catheterization unraveled precapillary PH, but thoracic CT scan and thoracocentesis excluded underlying pulmonary illness. Treatment continued at Gastroenterology department of tertiary hospital. Abdominal CT scan diagnosed cirrhotic liver, and signs of portal hypertension. The patient was treated with symptomatic therapy, but develop acute on chronic renal failure and eventually died.

Conclusion Multidisciplinary approach is very important to distinguish portopulmonary hypertension early in the course of liver disease, because evolution of right sided heart failure precludes these patients from adequate lifesaving therapy.

Keywords: pulmonary arterial hypertension; right-sided heart failure; liver cirrhosis

САЖЕТАК

Увод Плућна артеријска хипертензија и инсуфицијенција десне коморе су потенцијално фаталне компликације које могу настати код пацијената са портном хипертензијом. Циљ рада је приказати пацијента са завршним стадијумом болести јетре, портном и плућном артеријском хипертензијом и инсуфицијенцијом десног срца.

Приказ болесника Мушкарац, стар 57 година, примљен је на Клинику за кардиологију терцијерне болнице због знакова инсуфицијенције десног срца, асцитеса, плеуралних излива и претибијалних едема. Имао је историју злоупотребе алкохола, артеријске хипертензије и гихта. Непосредно пре пријема ултразвуком абдомена утврђена је зрнаста структура јетре, као и асцитес. Лабораторијски тестови су показали микроцитну анемију, вредности трансаминаза испод референтних, хипоалбуминемију и низак клиренс креатинина. Ехокардиографија је указала на плућну хипертензију и инсуфицијенцију десне коморе. Катетеризација десног срца открила је прекапиларну плућну хипертензију, али ЦТ преглед грудног коша и торакоцентеза су искључили постојање плућне болести. Лечење је настављено у Клиници за гастроентерологију терцијерне болнице. ЦТ-ом абдомена дијагностикована је циротична јетра и знаци портне хипертензије. Пацијент је лечен симптоматском терапијом, задобио је акутизацију хроничне бубрежне са смртним исходом.

Закључак Мултидисциплинарни приступ је веома важан за разликовање портопулмоналне хипертензије у раној фази болести јетре, јер појава десностране срчане инсуфицијенције онемогућава овим пацијентима адекватну терапију којом би се могао смањити морталитет.

Кључне речи: плућна артеријска хипертензија; десностране срчане инсуфицијенција; цироза јетре

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INTRODUCTION

Right-sided heart failure (RHF) clinical syndrome is associated with increased morbidity and mortality in a variety of diseases [1]. Heart failure and liver disease often coexist, because of bidirectional cardiohepatic interactions, concomitant risk factors or diseases affecting both organs [2]. RHF in patients with liver disease can be a consequence of cirrhotic

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cardiomyopathy, pulmonary vascular complications, concomitant left ventricular failure, and chronic renal failure [2-4]. Patients with portal hypertension can develop increased pulmonary vascular resistance (PVR) and pulmonary artery hypertension (PAH) condition called portopulmonary hypertension (PoHT) [3-9]. PoHT is frequently under recognized condition for a long time, with marked diagnostics and treatment variability [3-5, 8-12]. As pulmonary vascular resistance rises, right ventricle strain is raising, function declines with ultimate signs of RHF [1, 13]. Patients with advanced stage of PoHT usually have poor prognosis, frequent hospitalizations and high mortality from progressive RHF, acute renal failure, but the majority die of complications due to underlying decompensated liver failure [4, 11, 14].

The objective of this case report was to report a patient with end stage liver disease, portal and pulmonary artery hypertension and RHF.

CASE REPORT

A 57-year-old man was hospitalized for the first time in the Cardiology department of tertiary hospital, due to clinical signs resembling biventricular heart failure and NTproBNP above 25000 pg/mL, referred from pulmonologist. The patient presented with symptoms of dyspnea on minimal effort, and swellings of abdomen, scrotum and legs getting worse for last four weeks, weight loss10kg, and had several black stools seven days prior to admission. The patient had a history of untreated gout and arterial hypertension for last seven years, and without medical documentation. The patient did not smoke, but used alcohol almost every day, for last ten years. Just before the admission, the patient was examined by gastroenterologist. Abdominal ultrasound showed vast amount of ascites, enlarged spleen (156mm), small echogenic kidneys and bilateral pleural effusion; an elective gastroscopy was indicated. The patient was referred to pulmonologist, where chest radiography and diagnostic thoracentesis with evacuation of 1000ml of transudate was done, and the patient referred to cardiologist.

Physical examination on admission revealed that patient was afebrile, oxygen saturation 93%, skin was pale, sclera were normal staining, hypertensive 220/120mmHg, tachycardic 110/min, with bilateral jugular venous distention, accentuated pulmonic component of the second heart sound, tricuspid regurgitant holosystolic murmur, the right lung percussion dullness and absent breath sounds, as well as signs of ascites and pitting leg edema.

Baseline laboratory tests showed severe microcytic anemia (Hgb 73 g/l, MCV 67.9 fL), normal thrombocyte count, decreased level of liver transaminases (AST 7U/L, ALT 13U/L),

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normal bilirubin, mild direct hyperbilirubinemia (8μmol/L), elevated gamma-glutamyl transferase (78U/L), hypoalbuminemia (26g/L), INR value above referent (1.7), low creatinine clearance 32ml/min, hyperuricemia (652 μmol/L), as well as low levels of FT3 (3.73pmol/L), normal levels of FT4 (15.04 pmol/L) and high levels of TSH (10.43pmol/L). Serological tests for hepatitis B, hepatitis C and HIV were negative.

Transthoracic echocardiogram (TTE) revealed dilated right atrium (RAVs/BSA 43.68ml/m^2), tricuspid annulus (3.7cm), and right ventricle (RV1 4.7cm, RV2 2.6cm, RV3 8.6cm) (Figure 1), with flattening of interventricular septum (Figure 2), severe tricuspid regurgitation (TR) (Figure 3), high right ventricular systolic pressure 87mmHg (peak TR velocity 4.1 m/s), low tricuspid annular plane systolic excursion 1.4cm, and tricuspid annulus systolic velocity 0.08m/s) (Figure 4), no mitral regurgitation, mild pulmonic regurgitation, pulmonary artery diameter 2.4cm, and high inferior vena cava diameter 2.3cm, without inspiratory collapsibility. Left ventricle (LV) volumes were normal, with signs of concentric hypertrophy (diameters of interventricular septum 1.5cm, and posterior wall 1.5cm), preserved LV ejection fraction (EF 56%). Left atrium was dilated (LAVs/BSA 38.42ml/m^2). Ratio of peak early diastolic velocity (E) to peak velocity flow in late diastole (A) - E/A was 1.21, tissue Doppler imaging showed low septal early diastolic velocity (es') 0.06m/s, low lateral early diastolic velocity (el') 0.09m/s, with normal LV feeling pressure (E/e'av=9.3), diastolic dysfunction grade II, and minimal pericardial effusion.

Pulmonologist excluded active pulmonary disease based on the normal pulmonary parenchyma on thorax CT scan and bilateral transudative pleural effusions.

The patient was treated with red blood cells transfusion, albumin supplementation, parenteral diuretic therapy, therapeutic thoracentesis, antihypertensive therapy and thyroid hormone supplementation, but without improvement.

On the third day of hospitalization right heart catheterization was performed. The values indicated severe precapillary pulmonary arterial hypertension: mean pulmonary artery pressure (mPAP) 53mmHg; PVR 8.1 WU (703 Dynes/cm^5); pulmonary capillary wedge pressure (PCWP) 15mmHg, central venous pressure (CVP) 19mmHg, cardiac output (CO) 4.3L/min, and cardiac index (CI) 2.2 L/ml/m^2.

Given the history of untreated alcoholism, clinical signs of right heart failure, laboratory tests, TTE, abdominal ultrasound and right heart catheterization, the diagnosis of decompensated liver cirrhosis and portopulmonary hypertension in our patient was suspected.

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On the fourth day, treatment was continued in Gastroenterology department of tertiary hospital. Abdominal CT scan was done, revealing liver surface nodularity, portosystemic collaterals, splenomegaly, and ascites, thus confirming the diagnosis of portal hypertension and subsequent portopulmonary hypertension. The treatment was symptomatic, consisted of parenteral diuretics, albumins, red blood cells transfusions, several thoracentesis, and paracentesis. The patient developed acute on chronic renal failure, two continuous veno-venous hemofiltration was performed, but subsequently developed deterioration of hemodynamic status, and died after 35 days.

The study was approved by the Ethics Committee of the Institute for Cardiovascular Diseases of Vojvodina, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

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DISCUSSION

We reported the patient with alcohol-associated decompensated end-stage liver disease and pulmonary artery hypertension who presented with right heart failure. Almost 90% of the patients with cirrhosis eventually develop portal hypertension and this condition is crucial for the majority of complications, like PAH [4, 10-12, 15]. POPH is most commonly observed in the setting of cirrhosis, which is alcohol-associated in almost half of patients, as was the case in our patient [14].

Pathophysiology of pulmonary artery hypertension in the setting of portal hypertension is not clearly elucidated yet [4]. Proposed mechanism of pulmonary arterial changes are inflammation, endothelial dysfunction, smooth muscle proliferation and in situ thrombosis due to hyperkinetic circulation, endotoxemia, low liver clearance, and porto-systemic shunting of vasoactive peptides [4].

PoHT is usually asymptomatic for years [11]. As the disease progress and PVR rises, patients could have nonspecific clinical findings that could be mixed with signs of liver cirrhosis and include exertional or dyspnea at rest, palpitations, syncope, followed by signs of pulmonary and portal hypertension hypertension and eventually signs of RHF [11]. In our patient signs of RHF and portal hypertension were the first noted clinical signs. In a recent retrospective analisys of patients with PoHT, mean age at the time of death was 56.0 +/- 8.9 years, half of then were males, most of them were in New York Heart Association class III or IV, and had ascites, 25% had combined precapillary and postcapillary PH, as was in our case

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[14]. PAH directly caused death or contributed to death in 25% patients with PoHT, mainly from RHF [14]. Compared to patients with portal hypertension, patients with PoPH have more cardiac structural changes, like left and right atrial and ventricular enlargement, mitral and tricuspid regurgitation, pulmonary artery widening, pericardial effusion, and aortic regurgitation than those without PoPH [12, 16]. In our patient TTE revealed PH, normal values of estimated LV filling pressures, signs of RHF, small pericardial and pleural effusions were registered on admission, which all are associated with increased mortality [13, 17, 18].

Based on the initial echocardiographic finding, and clinical signs of liver cirrhosis, in order to diagnose PAH, right heart catheterization was done [19]. Our patient had high mPAP and PVR, but had concomitant chronic renal failure and left ventricle diastolic dysfunction leading to further volume overload. A mild elevation of PCWP with high level of PVR can be observed in some POPH patients with combined pulmonary vascular disease and a post-capillary component, due to increased left ventricular stiffness in the setting of high CO, and fluid overload [20]. But, transpulmonary gradient greater then 10, especially above 30, is suggesting the presense of increased pulmonary resistance, and is a predictor of poor prognosis, as was in our patient [21].

Our patient had hypothyroidism that could be a consequences of liver cirrhosis, especially alcoholic and/or PH, and presents a predictor of severity of liver disease and mortality [1].

Chronic kidney dysfunction (CKD) is common comorbidity associated with high mortality in patients with PH and CKD itself may cause pulmonary vascular remodelling [22]. According to Shao et al., compared to patients with portal hypertension, patients with POPH have lower hemoglobin and higher creatinine [12]. Our patient had pre-existing renal impairment due to long-term hypertension. Acute worsening of renal function in patients with PH is associated with RHF and mortality [23]. It has been shown that, aside systemic arterial hypoperfusion, venous congestion is a main driver for renal function deterioration in patients with RHF [23]. Our patient developed acute on chronic renal failure due to advanced liver disease per se, RHF, elevated intra-abdominal pressure, hypovolaemia, resulting from excessive diuretic use and large volume paracentesis and contrast agent given for CT scan.

Treatment of patients with POPH is usually late, complex and requires a multidisciplinary team, as was in our patient [11, 20, 24]. Mortality rate in untreated patients with POPH is high [25]. In a retrospective analysis conducted by Sahay et al. 33% patients with

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PoHT were considered unsuitable for liver transplantation because of uncontrolled PAH, as was in our patient [14].

Deroo et al. [26] recently shown that in patients with PoHT vasomodulatory therapy improves pulmonary hemodynamics and prolong survival, but if it is followed by liver transplantation could further improve prognosis.

In our case with portopulmonary hypertension, the first clinical presentation was right-sided heart failure. Early multidisciplinary approach, including using a transthoracic echocardiography is very important to distinguish portopulmonary hypertension early in the course of liver disease, because evolution of right sided heart failure precludes these patients from adequate lifesaving therapy.

Conflict of interest: None declared.

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REFERENCES

1. Thandavarayan RA, Chitturi KR, Guha A. Pathophysiology of acute and chronic right heart failure. Cardiol Clin 2020;38:149-60. doi: 10.1016/j.ccl.2020.01.009.
2. El Hadi H, Di Vincenzo A, Vettor R, Rossato M. Relationship between heart disease and liver disease: A two-way street. Cells 2020;9:567. [doi: 10.3390/cells9030567] [PMID: 32121065]
3. Soulaidopoulos S, Goulis I, Cholongitas E. Pulmonary manifestations of chronic liver disease: a comprehensive review. Ann Gastroenterol 2020;33:237-49. [doi: 10.20524/aog.2020.0474] [PMID: 32382226]
4. Peppas S, Nagraj S, Koutsias G, Kladas M, Archontakis-Barakakis P, Schizas D, Giannakoulas G, et al. Portopulmonary Hypertension: A Review of the Current Literature. Heart Lung Circ. 2022;31(9):1191-1202. [doi: 10.1016/j.hlc.2022.04.056] [PMID: 35667970]
5. Weinfurtner K, Forde K. Hepatopulmonary syndrome and portopulmonary hypertension: current status and implications for liver transplantation. Curr Hepatol Rep 2020;19:174-85. [doi: 10.1007/s11901-020-00532-y] [PMID: 32905452]
6. Thomas C, Glinskii V, de Jesus Perez V, Sahay S. Portopulmonary hypertension: from bench to bedside. Front Med (Lausanne) 2020;7:569413. [doi: 10.3389/fmed.2020.569413] [PMID:33224960]
7. DuBrock HM, Krowka MJ. The myths and realities of portopulmonary hypertension. Hepatology 2020;72:1455-60. [doi: 10.1002/hep.31415] [PMID: 32515501]
8. Raevens S, Geerts A, Devisscher L, Van Vlierberghe H, Van Steenkiste C, Colle I. Recent advances in the approach to hepatopulmonary syndrome and portopulmonary hypertension. Acta Gastroenterol Belg 2021;84(1):95-9. [doi: 10.51821/84.1.200] [PMID: 33639700]
9. Lai YK, Kwo PY. Portopulmonary Hypertension. Clin Liver Dis. 2023;27(1):71-84. [doi: 10.1016/j.cld.2022.08.002. [PMID: 36400468]
10. Navarro-Vergara DI, Roldan-Valadez E, Cueto-Robledo G, Jurado-Hernandez MY. Portopulmonary hypertension: prevalence, clinical and hemodynamic features. Curr Probl Cardiol 2021;46:100747. [doi: 10.1016/j.cpcardiol.2020.100747] [PMID: 33248724]
11. Lazaro Salvador M, Quezada Loaiza CA, Rodríguez Padial L, Barberá JA, López-Meseguer M, López-Reyes R, et al; REHAP Investigators. Portopulmonary hypertension: prognosis and management in the current treatment era - results from the REHAP registry. Intern Med J 2021;51:355-65. [doi: 10.1111/imj.14751] [PMID: 31943676]
12. Shao Y, Yin X, Qin T, Zhang R, Zhang Y, Wen X. Prevalence and associated factors of portopulmonary hypertension in patients with portal hypertension: A case-control study. Biomed Res Int 2021;2021:1-7. [doi: 10.1155/2021/5595614] [PMID: 33987440]
13. Cassady SJ, Ramani GV. Right heart failure in pulmonary hypertension. Cardiol Clin 2020;38:243-55. [doi: 10.1016/j.ccl.2020.02.001] [PMID: 32284101]
14. Sahay S, Al Abdi S, Melillo C, Newman J, Dweik RA, Heresi GA, Tonelli AR. Causes and circumstances of death in portopulmonary hypertension. Transplant Direct 2021;7:e710. [doi: 10.1097/TXD.0000000000001162] [PMID: 34124346]
15. Gunarathne LS, Rajapaksha H, Shackel N, Angus PW, Herath CB. Cirrhotic portal hypertension: From pathophysiology to novel therapeutics. World J Gastroenterol 2020;26:6111-40. [doi: 10.3748/wjg.v26.i40.6111] [PMID: 33177789]
16. Korbitz PM, Gallagher JP, Samant H, Singh S, Jophlin L, Ingviya T, Manatsathit W. Performance of echocardiography for detection of portopulmonary hypertension among liver transplant candidates: Meta-analysis. Clin Transplant 2020;34:e13995. [doi: 10.1111/ctr.13995] [PMID: 32485008]
17. Farmakis IT, Demerouti E, Karyofyllis P, Karatasakis G, Stratinaki M, Tsiapras D, Athanassopoulos G, Voudris V, Giannakoulas G. Echocardiography in pulmonary arterial hypertension: is it time to reconsider its prognostic utility? J Clin Med 2021;10:2826. [doi: 10.3390/jcm10132826] [PMID: 34206876]
18. Chandel A, Verster A, Rahim H, Khangoora V, Nathan SD, Ahmad K, et al. Incidence and prognostic significance of pleural effusions in pulmonary arterial hypertension. Pulm Circ 2021;11:1-10. [doi: 10.1177/20458940211012366] [PMID: 33996030]
19. Ghofrani HA. Cardiopulmonary haemodynamics in portopulmonary hypertension. Lancet Respir Med 2019;7: 556-8. [doi: 10.1016/S2213-2600(19)30143-2] [PMID: 31178423]

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20. Thévenot T, Savale L, Sitbon O. Portopulmonary hypertension: An unfolding story. Clin Res Hepatol Gastroenterol 2021;45:101492. [doi: 10.1016/j.clinre.2020.06.017] [PMID: 32800529]
21. Mazimba S, Mejia-Lopez E, Mejia-Lopez E, Black G, Kennedy JL, Bergin J, et al. Diastolic pulmonary gradient predicts outcomes in group 1 pulmonary hypertension (analysis of the NIH primary pulmonary hypertension registry). Respir Med 2016;119:81-6. [doi: 10.1016/j.rmed.2016.08.024] [PMID: 27692153]
22. Edmonston DL, Parikh KS, Rajagopal S, Shaw LK, Abraham D, Grabner A, Sparks MA, Wolf M. Pulmonary hypertension subtypes and mortality in CKD. Am J Kidney Dis 2020; 75:713-24. [doi: 10.1053/j.ajkd.2019.08.027] [PMID: 31732231]
23. Husain-Syed F, Gröne HJ, Assmus B, Bauer P, Gall H, Seeger W, et al. Congestive nephropathy: a neglected entity? Proposal for diagnostic criteria and future perspectives. ESC Heart Fail 2021;8:183-203. [doi: 10.1002/ehf2.13118] [PMID: 33258308]
24. DuBrock HM. Portopulmonary Hypertension: Management and Liver Transplantation Evaluation. Chest. 2023:S0012-3692(23)00043-0. [doi: 10.1016/j.chest.2023.01.009. [PMID: 36649754]
25. Swanson KL, Wiesner RH, Nyberg SL, Rosen CB, Krowka MJ. Survival in portopulmonary hypertension: Mayo Clinic experience categorized by treatment subgroups. Am J Transplant 2008;8:2445–53. [doi: 10.1111/j.1600-6143.2008.02384.x] [PMID: 18782292]
26. Deroo R, Trépo E, Holvoet T, De Pauw M, Geerts A, Verhelst X, et al. Vasomodulators and liver transplantation for portopulmonary hypertension: evidence from a systematic review and meta-analysis. Hepatology 2020;72:1701-16. [doi: 10.1002/hep.31164] [PMID: 32017176]

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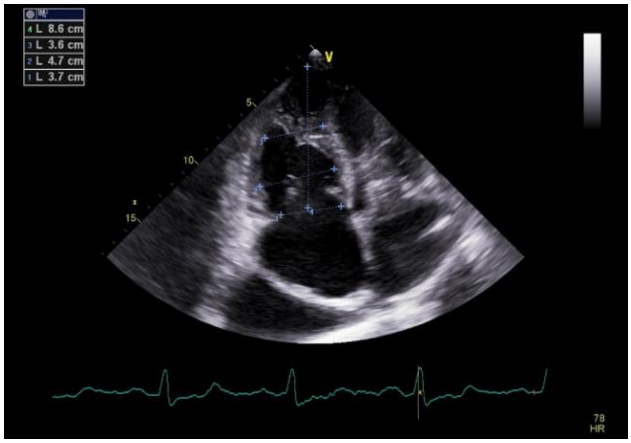

Figure 1. Dilated right atrium, tricuspid annulus and right ventricle

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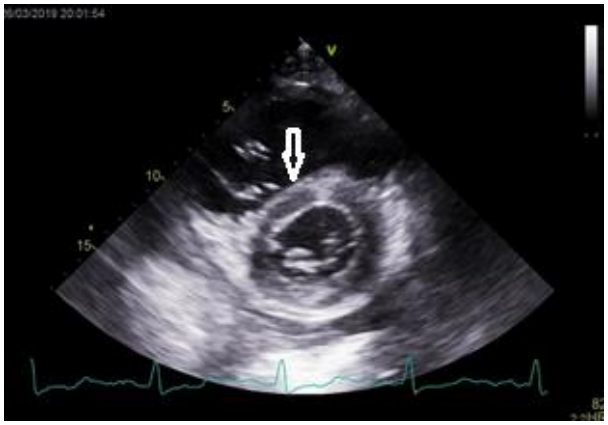

Figure 2. Flattening of interventricular septum in systole

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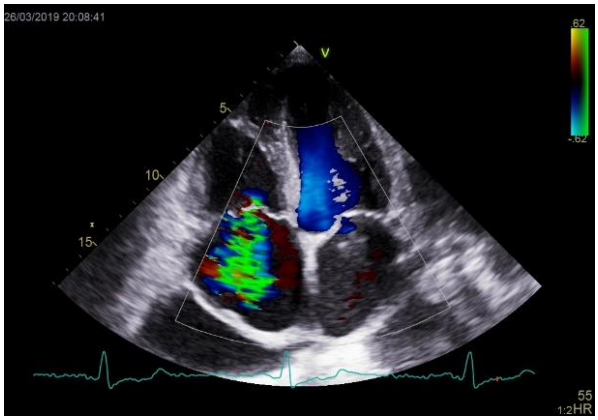

Figure 3. Severe tricuspid insufficiency

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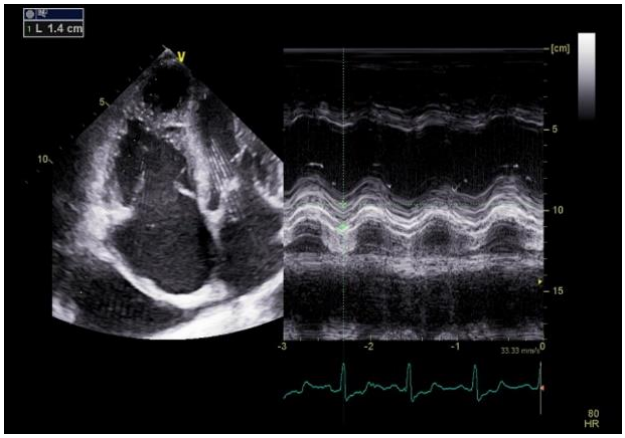

Figure 4. Low tricuspid annular plane systolic excursion (1.4 cm)

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