Development of Pulmonary Edema Despite Negative Fluid Balance with Diuretics in a Patient with Heart Failure and Sigmoid Septum

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An 87-year-old man was hospitalized due to dyspnea and leg edema. He was diagnosed with heart failure due to anemia with a hemoglobin (Hb) concentration of 6.0 g/dL. Chest X-ray on admission revealed pleural effusion. He was transfused with 400 mL packed red blood cells, which elevated the Hb concentration to 8.6 g/dL. Spironolactone (25 mg/day) and furosemide (20 mg/day, intravenously) were initiated. Despite the negative fluid balance, the patient's dyspnea worsened. Chest X-ray on day 8 revealed pulmonary edema despite decreased pleural effusion. Transthoracic echocardiography (TTE) revealed a sigmoid-shaped interventricular septum and systolic anterior motion of the mitral valve, causing left ventricular outflow tract obstruction (LVOTO; peak pressure gradient, 96 mmHg). Pilsicainide (75 mg/day) was administered to reduce the LVOTO. In addition, furosemide administration was changed to continuous infusion with increased dose of 48 mg/day (2 mg/h). The patient's dyspnea finally abated, with X-ray on day 12 revealing marked reduction in pulmonary congestion. TTE on day 17 revealed marked reduction in LVOTO (peak pressure gradient, 21 mmHg). Hemodynamic change by diuretics in the setting of right-sided heart failure due to anemia and in the presence of LVOTO due to sigmoid septum could be the cause of pulmonary edema.

Key words: Sigmoid septum, left ventricular outflow obstruction, pericardial constraint, heart failure

INTRODUCTION

Sigmoid septum is a morphological change of the heart in which the basal ventricular septum protrudes into the left ventricular outflow tract and has been thought to be a normal aging-related phenomenon [1, 2]. In some cases, sigmoid septum has been reported to cause significant left ventricular outflow tract obstruction (LVOTO), leading to hemodynamic compromise such as syncope [3], heart failure [4], and cardiogenic shock [5–9]. It was reported that among 73 patients with LVOTO with a pressure gradient of more than 50 mmHg at rest, 74% had obstructive hypertrophic cardiomyopathy, while 4% had sigmoid septum [10]. The LVOTO in obstructive hypertrophic cardiomyopathy and sigmoid septum is not due to organic or fixed lesions, but to functional and dynamic lesions which worsen with hemodynamic changes to reduce left ventricular volume such as reduced preload or afterload as well as augmented myocardial contractility [11, 12]. With regard to heart failure due to LVOTO with sigmoid septum, a case of congestive heart failure due to anemia was reported [4]. In that case, reduced afterload due to vasodilation of peripheral arteries and increased cardiac contraction due to augmented sympathetic activity, both of which are induced by anemia, could worsen LVOTO. Here we present a case of right-sided heart failure due to anemia and LVOTO with sigmoid septum, in which pulmonary edema was developed despite the negative fluid balance and decreasing pleural effusion with intravenous administration of loop diuretics. Hemodynamic changes after volume overload reduction of right-sided heart failure with diuretics in the presence of functional LVOTO with sigmoid septum could be a cause of left-sided heart failure and pulmonary edema.

CASE REPORT

An 87-year-old man with a history of cerebral hemorrhage and hepatic cirrhosis due to chronic hepatitis C was hospitalized due to dyspnea on effort and leg edema. The patient was found to have leg edema 2 years before admission and had been taking furosemide 10 mg per day. His leg edema had worsened 1 month before admission. On admission his blood pressure was 125/70 mmHg, and his heart rate was regular at 96 beats/min. Jugular venous distention with Kussmaul sign was observed in a sitting position. A grade 2/6 systolic murmur at the left sternal border in the third to fourth intercostal space was heard on auscultation. The patient had ascites and prominent leg edema. Chest X-ray showed bilateral pleural effusion with right side predominance (Fig. 1a). Laboratory data revealed pancytopenia, hypoalbuminemia, and renal dysfunction with a white blood cell count of 2200/μL, blood hemoglobin (Hb) concentration of 6.0 g/dL, platelet count of $8.2 \times 10^4/\mu$L, serum albumin concentration of 2.7 g/dL, and creatinine level of 1.54 mg/dL. The patient had microcytic hypochromic iron deficiency anemia and a fecal occult blood test was positive, therefore, oral iron supplementation (50 mg/day) was initiated. The patient was diagnosed with acute

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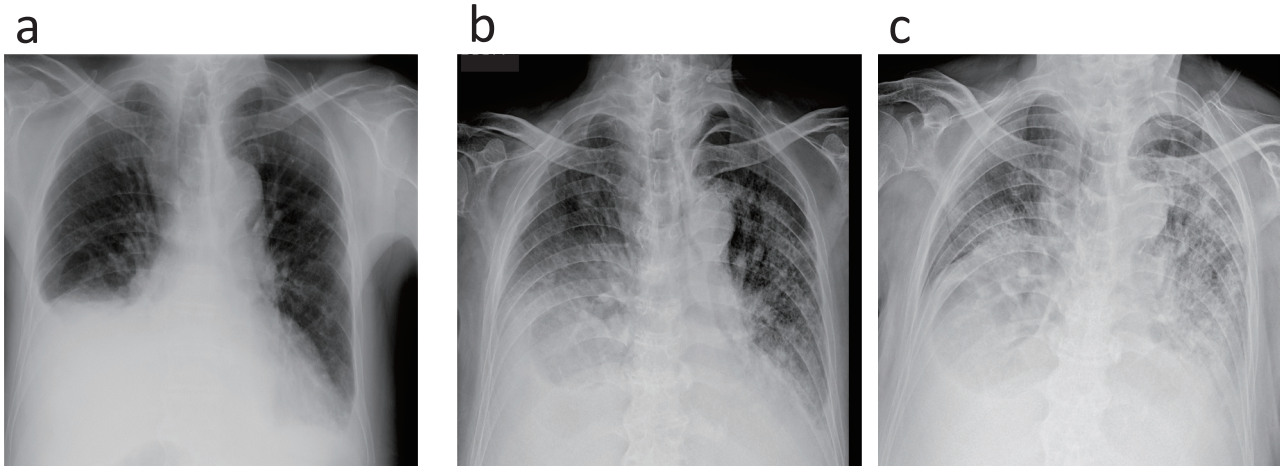

Fig. 1 Serial chest X-rays showing worsening of pulmonary congestion despite decreasing pleural effusion with diuretics. (a) On admission, chest X-ray revealed predominantly right-sided bilateral pleural effusion without pulmonary congestion. (b) On day 4, pulmonary congestion with cephalization of the pulmonary artery appeared, although pleural effusion was decreased. (c) On day 8, pulmonary congestion worsened and pulmonary edema was observed while pleural effusion was further decreased.

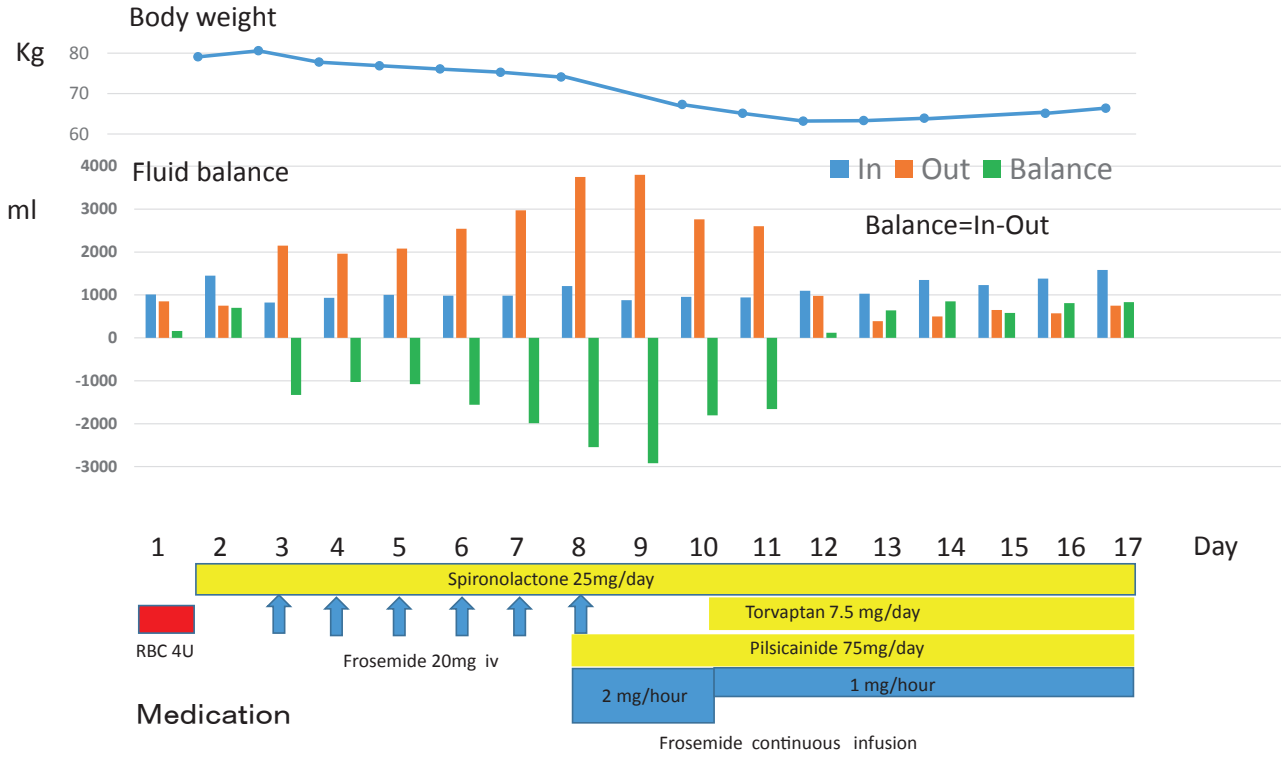

Fig. 2 Clinical course of the patient, including fluid balance and body weight.
Fluid balance remained negative with the use of diuretics, which was also indicated by a gradual decrease in body weight.

exacerbation of chronic heart failure due to anemia and transfused with 400 mL packed red blood cells, which elevated his Hb concentration to 8.6 g/dL. Oral administration of spironolactone (25 mg/day) and intravenous furosemide (20 mg/day) were initiated on day 2 and day 3, respectively. Fluid balance remained negative at −1000 to −3000 mL/day throughout the administration of diuretics, which reduced the volume overload, as indicated by a gradual decrease in body weight (Fig. 2). Despite this treatment the patient developed dyspnea. X-ray on day 4 revealed pulmonary congestion with cephalization of the pulmonary artery, although pleural effusion was decreased (Fig. 1b). Brain natriuretic peptide concentration was increased from 625 pg/mL on admission to 962 pg/mL on day 4. On day 8, X-ray revealed pulmonary edema despite decreasing pleural effusion (Fig. 1c). The Hb concentration was not changed (8.5 g/dL) but serum albumin concentration was reduced to 2.3 mg/dL. On auscultation, systolic murmur was augmented to grade 4/6. Two-dimensional and M-mode transthoracic echocardiography revealed a sigmoid-shaped

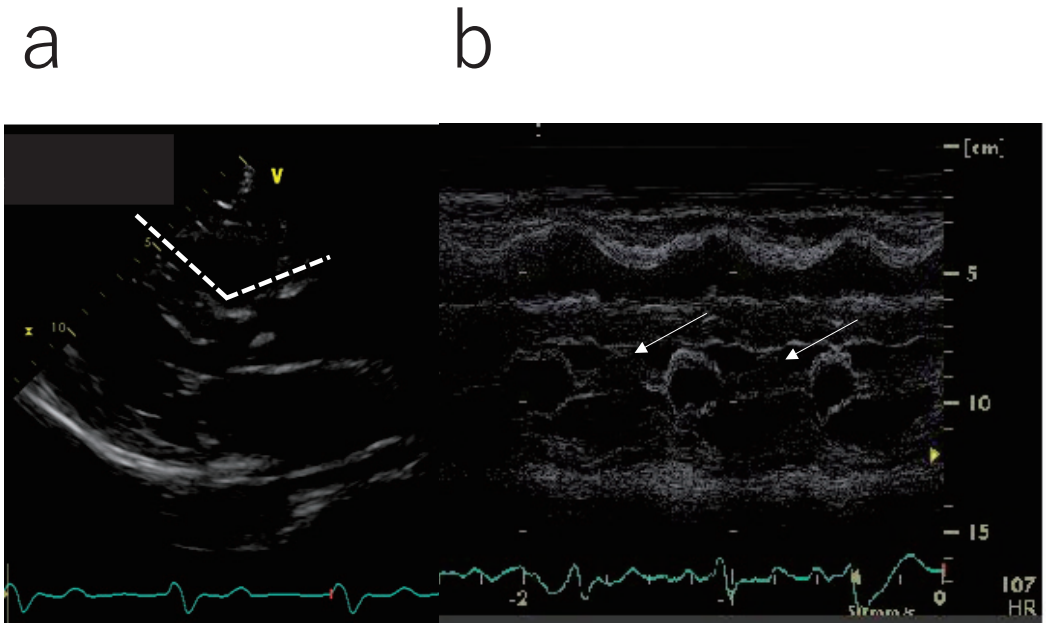

Fig. 3 (a) Two-dimensional transthoracic echocardiography performed on day 4 showing a decrease in angle between the anterior wall of the ascending aorta and ventricular septum (dashed line) with protruding basal septum which formed a sigmoid-shaped left ventricular outflow tract.
(b) M-mode echocardiography shows systolic anterior motion of the anterior mitral leaflet (arrows).

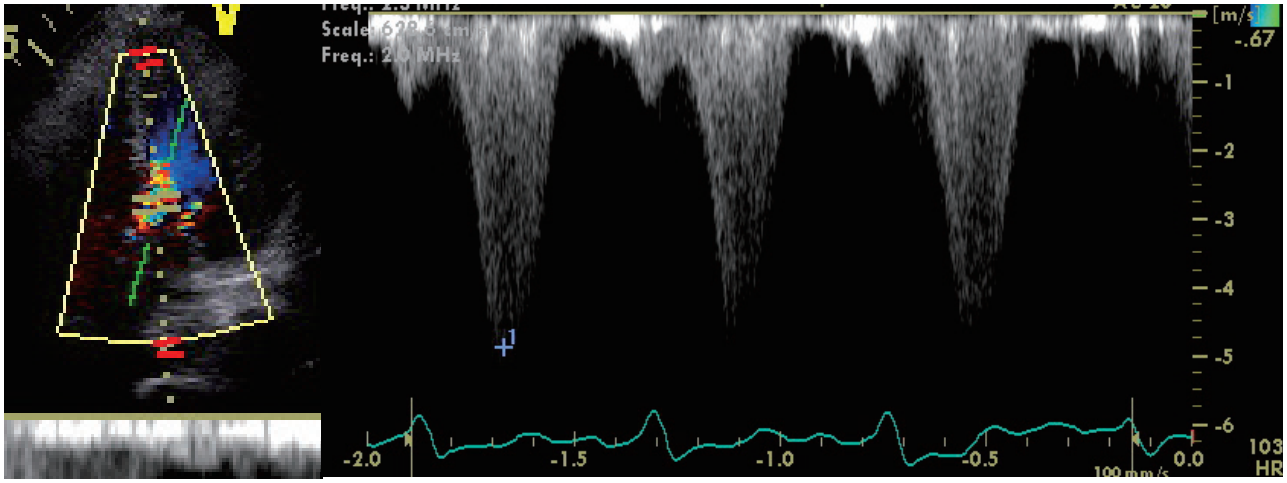

Fig. 4 Continuous-wave Doppler echocardiography along the left ventricular outflow tract revealed a peak flow velocity of 4.9 m/s (peak pressure gradient of 96 mmHg).

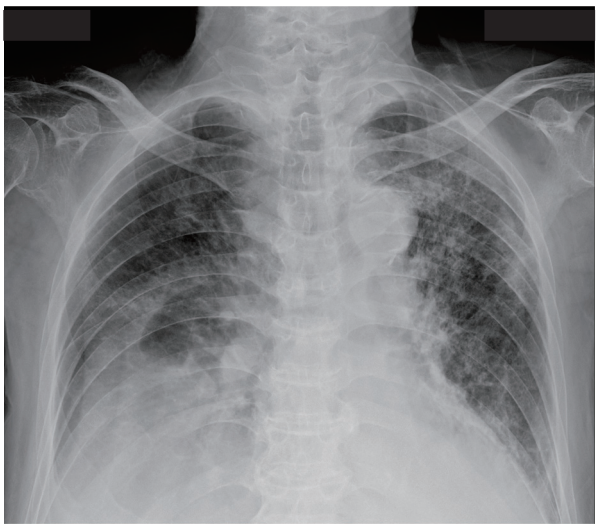

Fig. 5 After administration of pilsicainide (75 mg/day) and tolvaptan (7.5 mg/day), X-ray on day 12 revealed that pulmonary congestion and pleural effusion were both markedly reduced.

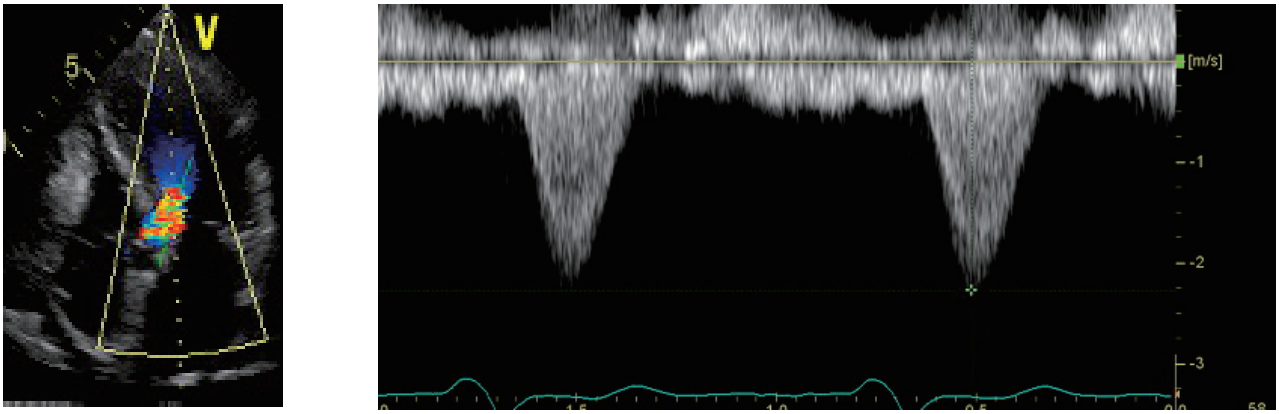

Fig. 6 Continuous-wave Doppler echocardiography on day 17 revealed a reduced left ventricular outflow tract obstruction of peak flow velocity of 2.3 m/s (peak pressure gradient of 21 mmHg).

interventricular septum (Fig. 3a) and systolic anterior motion (SAM) of the mitral valve (Fig. 3b), respectively. Continuous-wave Doppler echocardiography across the left ventricular outflow tract revealed a peak flow velocity of 4.9 m/s (peak pressure gradient 96 mmHg) (Fig. 4). Thickness of the interventricular septum and the posterior wall of the left ventricle, left ventricular end-diastolic dimension, left ventricular end-systolic dimension, and left ventricular ejection fraction (EF) were 12.1 mm, 7.8 mm, 44.6 mm, 32.6mm, and 53.9%, respectively, which indicated that LVOTO was not due to hypertrophic cardiomyopathy and the type of heart failure was compatible with heart failure with preserved EF. Accordingly, pilsicainide (75 mg/day) was administered to reduce LVOTO. In addition, administration of furosemide was changed to continuous infusion and the dose was increased to 48 mg/day (2 mg/h). Because of progression of hyponatremia (139 mEq/L on admission; 130 mEq/L on day 10), the infusion rate of furosemide was reduced to 1 mg/h and 7.5 mg tolvaptan was added on day 10. The patient's dyspnea was relieved, with X-ray on day 12 revealing that pulmonary congestion and pleural effusion were both markedly reduced (Fig. 5). Continuous-wave Doppler echocardiography on day 17 revealed a reduced LVOTO of peak pressure gradient of 21 mmHg (Fig. 6). Regarding the anemia, after transfusion of 400 mL packed red blood cells on admission, the Hb level was maintained around 9 g/dL with oral iron supplementation. However, on day 23 the patient had tarry stools and the Hb level dropped to 7.4 g/dL. The patient was transfused with 400 mL packed red blood cells and underwent emergency endoscopic examination, which revealed active bleeding from gastric erosion. The patient was treated successfully.

DISCUSSION

The unexpected finding of the present case was that, while pulmonary effusion was reduced by diuretic administration, which was consistent with negative fluid balance and decreasing body weight, pulmonary congestion worsened, leading to the development of pulmonary edema. The worsening of dynamic LVOTO, which had been induced by anemia in the presence of sigmoid septum and the hemodynamic change induced by administration of a diuretic in the setting of right-sided heart failure, was thought to be the underlying cause of pulmonary edema.

Goor *et al.* first reported sigmoid septum as a common variation in the contour of the left ventricular outlet [1]. The authors studied necropsy specimens from 44 normal subjects and found sigmoid septum in 25 of 34 (74%) subjects over 50 years of age. Sigmoid septum has been thought to be associated with normal aging and to have no pathological significance. However, in the presence of predisposing factors, LVOTO due to sigmoid septum has been reported to induce significant hemodynamic compromise such as syncope [3], heart failure [4], and cardiogenic shock [5–9]. The same mechanism underlying obstructive hypertrophic cardiomyopathy is thought to account for the LVOTO induced by sigmoid septum, because mitral SAM is observed in both settings. The mechanism of LVOTO induced by SAM has been studied in patients with hypertrophic cardiomyopathy [13–15]. In hypertrophic cardiomyopathy, anterior and internal displacement of papillary muscle occurs, which positions mitral leaflets anterior to the left ventricular outflow tract so that blood flow pushes the leaflets into the outflow tract causing SAM and subsequent LVOTO [13, 14]; this mechanism is known as the drug effect. Regarding the mechanism of LVOTO by sigmoid septum, a rightward shift of the dilated ascending aorta and a leftward shift of the basal ventricular septum occur during aging, resulting in bulging of the basal ventricular septum into the left ventricular outflow tract [1, 2], which positions the mitral leaflets in the sigmoid shaped outflow of the left ventricle. Decreased left ventricular size, especially in the direction of the long axis, also occurs with aging [2], making the mitral leaflets and chordae tendineae redundant, thereby promoting SAM.

In obstructive hypertrophic cardiomyopathy, reduced preload or afterload leads to reduction of left ventricular volume, which increases redundancy of the mitral leaflets and chordae tendineae, thereby augmenting SAM and LVOTO. Increased myocardial contractility also augments LVOTO by increasing the drug force. The same hemodynamic changes that increase LVOTO of obstructive hypertrophic cardiomyopathy have been reported to worsen LVOTO in the setting of sigmoid septum [8, 15].

In subjects with sigmoid septum, syncope was reported after intake of alcohol or sublingual nitroglycerin [3]. In these cases, vasodilation with alcohol or nitroglycerin acts as a predisposing factor for LVOTO

by reducing both preload and afterload of the left ventricle.

In the setting of intensive care patients with hypotension including septic shock, use of inotropic agents in the presence of hypovolemia can induce significant LVOTO in susceptible patients including those with sigmoid septum [5, 6]. In such cases, stopping inotropic agents, and fluid administration with or without vasoconstrictive agents, will restore blood pressure whereas increasing the dose of inotropic agents will further worsen the hemodynamic state, resulting in a potentially fatal vicious cycle. In cases of acute myocardial infarction or takotsubo cardiomyopathy, compensatory hypercontraction of the base of the left ventricle can induce LVOTO and subsequent cardiogenic shock [7–9]. In these cases, vasoconstrictive agents instead of inotropic agents should also be considered.

LVOTO induced by anemia in the presence of sigmoid septum was reported as a cause of congestive heart failure [4]. In this case, reduced afterload due to vasodilation of peripheral arteries [16] and increased cardiac contraction due to augmented sympathetic activity [17], both of which are induced by anemia, were considered the potential causes of worsening LVOTO.

In the present case of a patient with LVOTO due to sigmoid septum and right-sided heart failure due to anemia, pulmonary congestion worsened and pulmonary edema developed despite the negative fluid balance and decreasing pleural effusion with diuretics. Cases of acute pulmonary edema after pericardiocentesis for cardiac tamponade have been reported [18, 19]. In these cases, a sudden increase of right ventricular output and pulmonary venous return to the left ventricle after release of pericardial constraint which caused tamponade has been proposed as one of the underlying mechanisms. The role of pericardial constraint in the pathophysiology of heart failure has been reported [20, 21]. In patients with heart failure, as the volume of the heart increases normal pericardium becomes constrained and disturbs the diastolic function of the ventricles. In right-sided heart failure, the left ventricle becomes under-filled despite the marked increase in left atrial and left endo-diastolic pressure because of increased pericardial pressure due to the increased volume of the right ventricle. In this setting, reduction of volume overload of the right ventricle can paradoxically increase right ventricular output and pulmonary venous return to the left ventricle. It was reported that in 24 patients with refractory heart failure removal of more than 4L of fluid by extracorporeal ultrafiltration over a period of a few hours increased cardiac output from around 3.5 L/min at baseline to more than 4 L/min at 24 h after the treatment [22]. The authors of this study speculated that this paradoxical increase of cardiac output might be due to a reduction of the extracardiac constraint, because the right and left atrial pressures were reduced by the same extent (i.e., according to the report, right and left atrial pressures were reduced in a 1-to-1 rather than the usual 1-to-3 ratio) throughout the treatment and 24 h after treatment. In another study, in 9 of 21 patients with chronic heart failure, mechanical volume unloading of the right ventricle via lower-body suction with a negative pressure of 30 mmHg paradoxically increased the left ventricular end-diastolic volume by decreasing the right ventricular end-diastolic volume [23].

In the present case, the presence of pericardial constraint was indicated by jugular venous distention with Kussmaul sign; therefore, removal of pericardial constraint by diuretics could have caused the increase of pulmonary venous return to the left ventricle. This mimics the hemodynamic changes of pulmonary edema after pericardiocentesis for cardiac tamponade, resulting in pulmonary edema in the setting of LVOTO due to sigmoid septum.

CONCLUSIONS

A case of development of pulmonary edema in a patient with right-sided heart failure due to anemia and LVOTO due to sigmoid septum despite negative fluid balance with diuretics was presented. Hemodynamic change after removal of pericardial constraint by diuretics in the presence of LVOTO due to sigmoid septum could be the cause of pulmonary edema.

CONFLICT OF INTEREST

There were no conflicts of interest.

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