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Protein-losing Enteropathy in Association with Right Heart Failure

Takanobu Hirosawa[1], Kazuhito Hirata[1,*], Wake Minoru[2]

[1]Division of Internal Medicine, Okinawa Chubu Hospital, 281 Miyazato, Uruma, Okinawa, Japan
[2]Division of Cardiology, Okinawa Chubu Hospital, 281 Miyazato, Uruma, Okinawa, Japan
*Corresponding author: kheart911@yahoo.co.jp

Abstract A 65-year-old woman, with past history of mitral valve replacement, developed severe right heart failure. In addition to elevated right heart pressure, she had significant hypoalbuminemia as the important cause of refractory edema. Technetium-99m-labelled human serum albumin scintigraphy showed leak of protein from the transverse colon and the excretion of alpha 1 antitrypsin in the stool was markedly increased. Diagnosis of protein losing enteropathy was established. The etiology was increased lymphatic pressure secondary to right heart failure of multifactorial cause, including elevated left side filling pressures and out of proportion pulmonary hypertension due to old tuberculosis, resulting in significant tricuspid regurgitation. The patient was managed conservatively with increased dose of furosemide from 10-20mg every other day up to 40-60mg/day, and maximum dose of tolvaptan (a vasopressin 2 receptor blocker) of 15mg/ day, in addition to high protein diet.

Keywords: *protein losing enteropathy, right heart failure, tolvaptan*

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1. Introduction

Protein losing enteropathy (PLE) is a rare condition of gastrointestinal protein loss that is caused by a variety of diseases. The primary cause can be divided into erosive gastrointestinal disorders, non-erosive gastrointestinal disorders, and disorders involving increased central venous pressure, such as right heart failure (RHF) [1]. Reported cause of RHF included advanced congestive heart failure [1,2], post-Fontan procedure [3], constrictive pericarditis [4,5] and tricuspid regurgitation [6] etc. We present a case of PLE in which hypoalbuminemia was caused by significant loss of serum protein from the colon in association with right heart failure of multifactorial origin. Tolvaptan, a vasopressin 2 receptor blocker, appeared to be very effective to control refractory edema and hypoproteinemia.

2. Case Presentation

A 65-year-old woman was hospitalized for evaluation of refractory edema. She had been well until 20 months prior to admission when she started to notice bilateral leg edema and worsening of dyspnea. She gradually gained weight, from 47kg to 56kg. She denied nausea, vomiting, or diarrhea.

Her past history was remarkable for mitral valve replacement (mechanical bi-leaflet valve) for rheumatic mitral stenosis 20 years before admission, chronic atrial fibrillation, and old tuberculosis (TB) in the right lung and pleura. She frequently had episodes of bacterial pneumonia every winter for recent years and had episode of actinomycosis in the uterus 18 months prior to admission.

Her medications included furosemide, spironolactone, warfarin, digoxin, allopurinol, and pitavastatin.

She had been stable with small amount of diuretics (furosemide 10-20mg every other day), but after she noticed worsening of edema, the dose of furosemide was increased up to 40-60 mg/day and finally, tolvaptan 7.5mg (vasopressin 2 receptor blocker) was required to control refractory edema.

While medical treatment was attempted in the clinic, she was evaluated with echocardiography and CT scan for possible prosthetic mitral valve dysfunction, worsening of systolic left ventricular function (LVF), and constrictive pericarditis. But the results were not conclusive. Blood test revealed significant hypoalbuminemia (total protein (TP) of 4.9 g/dl, albumin (ALB) of 2.7g/dl: normal ranges are 6.7-8.3g/dl and 3.8-5.3g/dl, respectively), whereas there was no loss of protein in the urine. Production of ALB was preserved as shown by normal pre-albumin level of 23.5mg/dl (18-34.7). Two years ago, TP and ALB were 6.6g/dl and 3.7g/dl, respectively. Electrolytes, kidney and liver functions were as follows: Sodium 140 mEq/l, potassium 4.3 mEq/l, Chloride 104 mEq/l, urea nitrogen 17 mg/dl, creatinine 0.71 mg/dl, AST 40 IU/l (10-34), ALT 24 IU/l (7-35), LDH 420 IU/l (107-220), direct bilirubin of 0.4mg/dl (<0.4) and total bilirubin of 1.3mg/dl (<1.2mg/l). Mild elevation of AST, LDH and indirect bilirubin was attributed to mild hemolysis. Complete

blood counts showed the following values: hemoglobin of 14.0g/dl, hematocrit of 43%, platelets of 116,000/µl, white blood cell of 5,300/µl with 17.0% lymphocytes (absolute lymphocyte count of 901/µl: normal>1000/µl). She continued to have hypoalbuminemia consistently with an albumin level of 2.5g/dl.

So, she was hospitalized for evaluation. Her vital signs at the time of admission were as follows: blood pressure of 122/52 mmHg, heart rate of 76/min, irregularly irregular, respiratory rate of 16 /min, and arterial oxygen saturation of 96 % under room air. Her jugular vein was markedly distended and elevated up to the jaw level with prominent v- wave in the upright position and her legs were edematous. Auscultation of the heart revealed pan-systolic murmur at 4th left sternal border. A chest roentgenogram revealed cardiomegaly and decreased permeability in the right lower lung field due to old TB (Figure 1 A). A 12-lead electrocardiogram showed atrial fibrillation, ST-T changes with U wave, and high voltage (Figure 1 B). A trans-thoracic echocardiogram (Figure 2B) showed preserved LVF, normal mitral prosthesis, moderate severe tricuspid regurgitation and pulmonary hypertension (PH: estimated right ventricular systolic pressure of 52 mmHg). Thickening of the pericardium was not apparent. Trans-esophageal echocardiogram did not show prosthetic mitral valve dysfunction or regurgitation. A contrast-enhanced CT of the chest and abdomen revealed scattered calcification in the wall of the atria (Figure 2B: right atrial calcification was more prominent than left atrium), and thickening of the wall of transverse colon. There was no thickening or calcification of the pericardium. There were no thrombi in the pulmonary circulation or no findings suggestive of chronic thromboembolic pulmonary hypertension. Pulmonary function tests confirmed the restrictive pattern with forced expiratory volume in 1 s (FEV_1) 1.0 L (55% of predicted), forced vital capacity (FVC) 1.3 L (55%), FEV_1/FVC 77%. Cardiac catheterization (Figure 3) revealed the following results: aorta: 150/73 (mean=104) mmHg and left ventricle: 150/0-16 mmHg, right atrium: 12 mmHg (v wave of 16 mmHg), right ventricle: 60/2-12 mmHg, pulmonary artery: 60/28 (mean=38) mmHg, and pulmonary capillary wedge pressure (WP): 18 mmHg; cardiac output: 5.30 l/min. Although there was a dip and plateau pattern in both right and left ventricle, end-diastolic pressures were not equalized in four chambers (Figure 3). A trans-pulmonary pressure gradient (TPG) was 20 mmHg (< 12mmHg), and diastolic pulmonary vascular pressure gradient (DPG) was 10mmHg (< 7 mmHg). Left ventriculography revealed normal wall motion with an ejection fraction of 60 %. There was no significant stenosis in coronary arteries.

Because there was no loss of protein in the urine and the production of the protein was preserved, PLE was suspected as the cause of hypoproteinemia. In order to prove this hypothesis, Technetium-99m-labelled human serum albumin scintigraphy was performed. There was a definite loss of albumin from the transverse colon (Figure 4). Moreover, Alpha-1 antitrypsin excretion in the stool was markedly elevated up to 906mg/day (normal < 27 mg/day [6]). Endoscopic evaluation of the upper and lower intestinal tract with multiple biopsy did not show histopathologic abnormality. Decreased production of the protein in the liver due to chronic congestion was considered less likely because pre-albumin was normal and markers of liver cirrhosis was negative and the liver biopsy performed at the time of cholecystectomy several months later did not show histological evidence of liver cirrhosis.

We offered possible pericardiectomy and tricuspid valve repair or replacement as a therapeutic option, although the risk of surgery was estimated to be relatively high due to second surgery and impaired lung function. The patient was reluctant to have the surgical therapy, so she was managed medically with high protein diet (2g/kg/day) and increasing the dose of tolvaptan up to 15 mg (maximum dose). Fortunately, she responded to these treatments. Leg edema improved, her body weight returned to the usual level and jugular venous pressure was markedly improved. Two months later, her TP and ALB increased up to 6.6g/dl and 3.7g/dl, respectively.

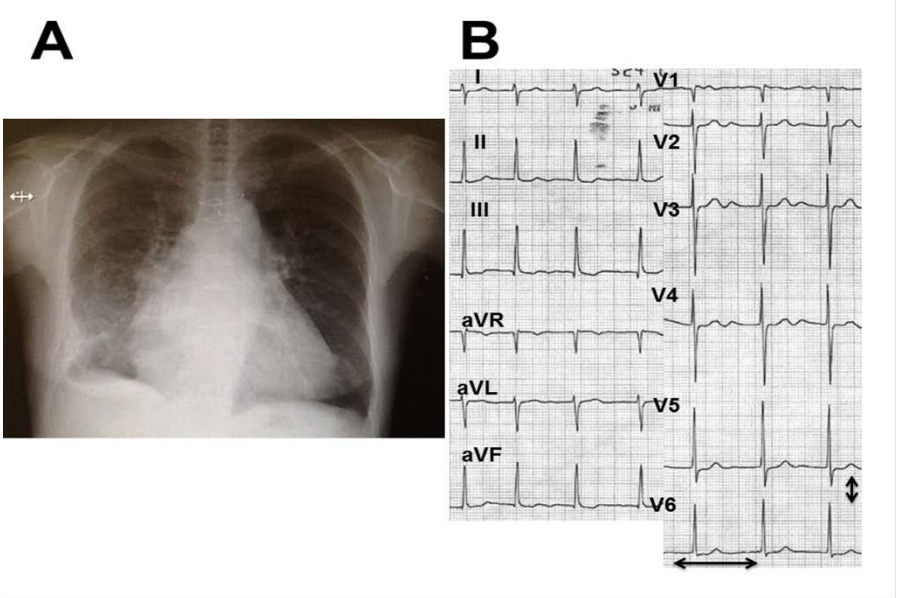

Figure 1. A: A chest roentgenogram showed cardiomegaly, parenchymal lung disease and old pleurisy in the right lower lung field. B: A twelve-lead electrocardiogram showing atrial fibrillation, right axis deviation, and high voltage in the left precordial leads

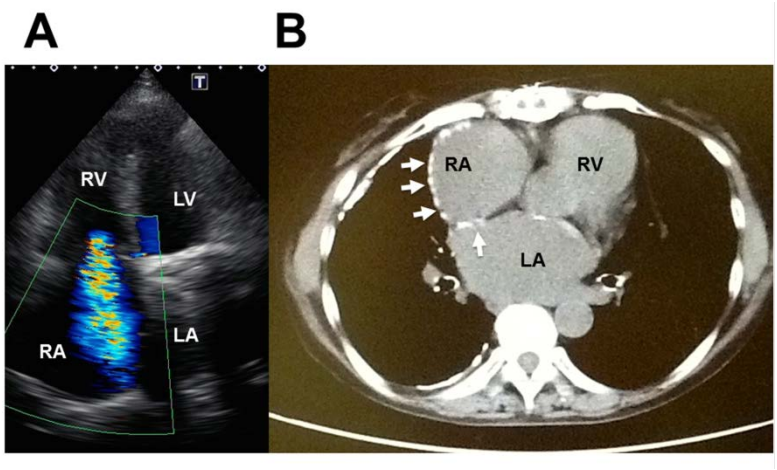

Figure 2. A: Apical 4-chamber views showing dilatation of right atrium, and moderate-severe tricuspid regurgitation by color Doppler. RV: Right ventricle, RA: Right atrium, LV: Left ventricle, LA: Left atrium. B: A chest CT revealed scattered calcification in the wall of the atria (arrows). There was no thickening of the pericardium. RV: Right ventricle, RA: Right atrium, LA: Left atrium

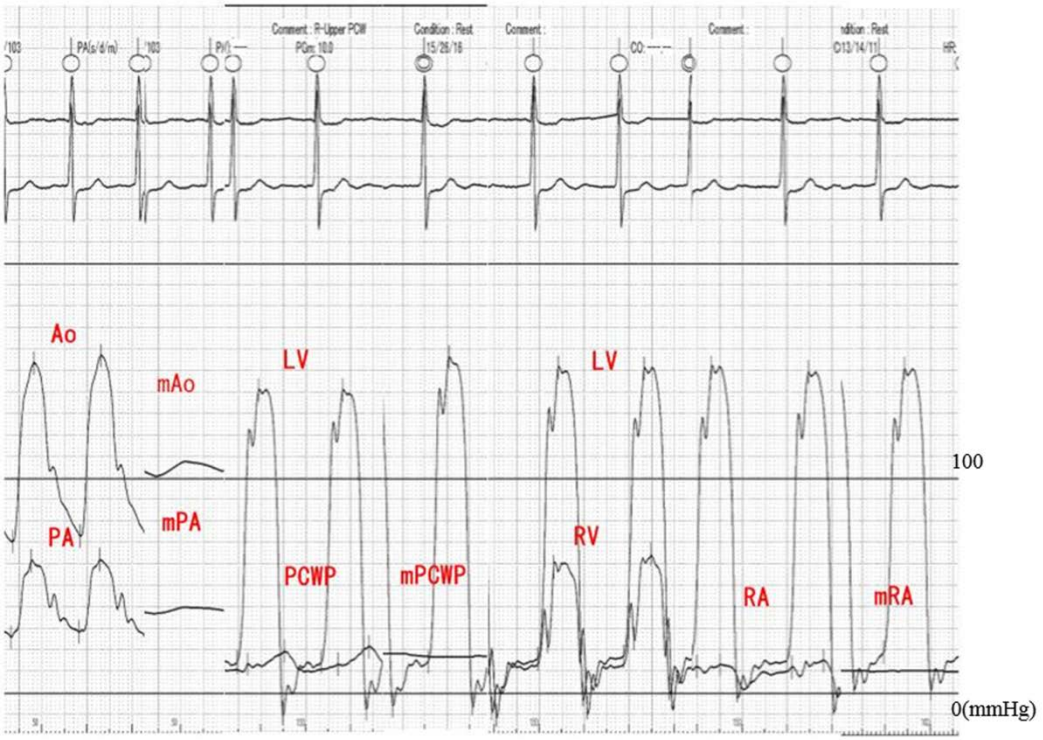

Figure 3. Simultaneous pressure recordings during cardiac catheterization. See text in detail. Ao: Aorta, LV: Left ventricle, PA: Pulmonary artery, PCWP: Pulmonary capillary wedge pressure, RV: Right ventricle, RA: Right atrium, Small letter "m" indicates mean pressure

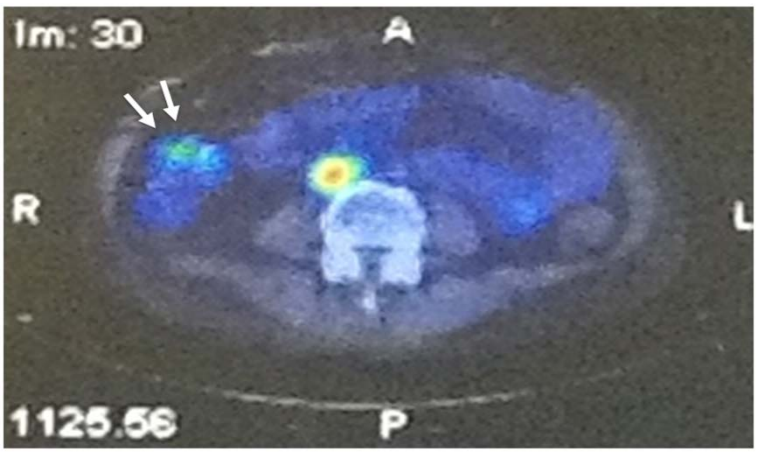

Figure 4. Technetium-99m-labelled human serum albumin scintigraphy showing a leak from the transverse colon (arrows)

3. Discussion

In this particular patient, hypoalbuminemia was caused by PLE as shown by markedly increased excretion of alpha 1 antitrypsin [7], which has a moderately higher molecular weight than albumin (50,000) and is excreted intact in the stool and is resistant to degradation in the intestinal lumen. Although a biopsy did not show histological findings such as lymphangiectasis, loss of protein from the transverse colon was clearly shown by Technetium-99m-labelled human serum albumin scintigraphy [8]. The association of PLE with cardiac disease was first described in 1961 by Davison et al [2]. To date, reported cardiac diseases related to PLE included congestive heart failure [1,2], post repair of complex congenital heart diseases (Fontan procedure) [3], constrictive pericarditis [4,5], tricuspid regurgitation [6] etc. All of these conditions were associated with increased right side pressure due to RHF. Decreased lymphatic drainage due to high venous pressure is considered the underlying mechanism for intestinal loss of protein [1].

In the present case, pathophysiology of RHF appeared to be complex and multifactorial. We initially considered the possibility of constrictive pericarditis and prosthetic mitral valve dysfunction, which can be surgically correctable. However, there was no prosthetic dysfunction by echocardiogram. CT scan did not show thickened pericardium, and cardiac catheterization showed equivocal results for constriction (discrepancy of RA and WP>5mmHg, PH). WP and left ventricular end-diastolic pressure were elevated but systolic LVF was normal (suggesting diastolic dysfunction of LV). So, PH was partly passive due to elevated left heart pressures. However, the degree of PH was out of proportion to elevated WP (TPG of 20mmHg and DPG of 10mmHg) [9]. Because there was no evidence of chronic thromboembolic PH or other causes of PH such as medication, parasite or liver cirrhosis etc, we concluded that parenchymal lung disease due to old TB (post tuberculosis lung destruction in the right middle and lower lobe) contributed to her out-of-proportion PH. Pulmonary hypertension and possible chronic tricuspid valvulitis due to rheumatic disease resulted in significant tricuspid regurgitation, leading to severe right heart failure. Moreover, stiff atria as suggested by scattered calcium deposit in the atrial wall (coconuts atrium) contributed to the elevation of right atrial pressure due to loss of compliance resulting in higher right atrial pressure for given degree of tricuspid regurgitation [10]. All of these factors may have contributed to RHF, which then contributed to secondary PLE leading to refractory edema.

Patient with longstanding RHF may develop congestive liver cirrhosis resulting in decreased production of proteins. However, pre-albumin level was preserved in this patient, meaning that protein synthesis was normal. Moreover, liver biopsy performed at the time of cholecystectomy, several months later, did not show cirrhosis, either. So, decreased production was not a likely cause of hypoalbuminemia in this patient.

The patients with PLE were known to develop immunological compromise, because immunoglobulins and lymphocytes were also lost from the gastrointestinal tract [8]. The present case did have lymphopenia. Frequent episodes of bacterial pneumonia and uterine aspergillosis might have been related to PLE.

Tolvaptan, a vasopressin 2 receptor blocker, is a novel and very potent diuretics, and is very effective if usual dose of furosemide was not effective [11]. Increasing the tolvaptan up to maximal dose resulted in marked improvement of right heart failure and hypoproteinemia in this patient.

In conclusion, the possibility of PLE should always be considered whenever hypoproteinemia is accompanied with RHF. Every effort including surgery should be undertaken to improve RHF and lower central venous pressure.

Conflict of Interest

Authors have no conflict of interest regarding this case report.

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