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Pulmonary hypertension, nephrotic syndrome, and polymyositis due to hepatitis C virus infection: a case report and literature review

Pulmonary hypertension caused by hepatitis C

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Abstract

BACKGROUND

Hepatitis C infection not only damages the liver but also often accompanies many extrahepatic manifestations. Incidences of pulmonary hypertension caused by hepatitis C are rare, and incidences of concurrent nephrotic syndrome and polymyositis are even rarer.

CASE SUMMARY

Herein we describe the case of a 57-year-old woman who was admitted to our department for intermittent chest tightness upon exertion for 5 years, aggravated with dyspnea for 10 days. After relevant examinations she was diagnosed with pulmonary hypertension, nephrotic syndrome, and polymyositis due to chronic hepatitis C infection. A multi-disciplinary recommendation was that the patient should be treated with sildenafil and macitentan in combination and methylprednisolone. During treatment autoimmune symptoms, liver function, hepatitis C RNA levels, and cardiac parameters of right heart catheterization were monitored closely. The patient showed significant improvement in 6-minute walking distance from 100 to 300 m at 3-month

follow-up and pulmonary artery pressure drops to 50 mmHg. Long-term follow-up is needed to confirm further efficacy and safety.

CONCLUSION

Increasing evidence supports a relationship between hepatitis C infection and diverse extrahepatic manifestations, but it is very rare to have pulmonary hypertension, nephrotic syndrome, and polymyositis in a single patient. We conducted a literature review on the management of several specific extrahepatic manifestations of hepatitis C.

Key Words: Keywords: case report; hepatitis C; nephrotic syndrome; polymyositis; pulmonary hypertension

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Core Tip: Core tip: Hepatitis C virus infection should be considered a systemic disease which is often associated with many extrahepatic manifestations, but it is very rare to have multiple different extrahepatic manifestations in a single patient. In this article, we report a case of pulmonary hypertension, nephrotic syndrome, and polymyositis due to hepatitis C virus infection. The optimal treatment strategy for hepatitis C-related extrahepatic manifestations remains to be determined. Our case confirms sildenafil and macitentan as effective treatment option for patients suffering from pulmonary hypertension due to hepatitis C infection. However, randomized, controlled trials are warranted to confirm the present results.

INTRODUCTION

Hepatitis C virus (HCV) is a sporadic and a common cause of chronic hepatitis after blood transfusion. In recent years various authors have described associations between

hepatitis C infection and a heterogeneous group of non-hepatic diseases such as cryoglobulinemia, rheumatoid arthritis, Sjogren's syndrome, and glomerulonephritis, which are seen as extrahepatic manifestations of chronic hepatitis C infection [1].

⁷ Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) ≥ 20 mmHg at rest with right heart catheterization [2]. ⁵ PH affects approximately 1% of the global population, up to 10% of individuals aged ≥ 65 years, and at least 50% of patients with heart failure [3]. PH has several different causes with different management and outcomes. However, PH due to hepatitis C has rarely been reported. Herein we describe a case of PH, nephrotic syndrome, and polymyositis following chronic hepatitis C infection in a 57-year-old woman.

CASE PRESENTATION

Chief complaints

A 57-year-old Chinese woman presenting with untreated chest tightness, shortness of breath, and fatigue for 5 years and with dyspnea for 10 days was admitted to the China-Japan Union Hospital of Jilin University.

History of present illness

She had no precordial pain, orthopnea, or palpitation. She had no joint pain, dental ulcers, or rash.

History of past illness

Forty years previously she had received an intravenous blood transfusion for a right ovariectomy. Sixteen years previously she was diagnosed with hepatitis C, nephrotic syndrome, and hypertension, but did not receive standard treatment. Five years previously she developed mild PH with pulmonary arterial pressure of 54 mmHg measured by transthoracic echocardiography, which was not treated further. Three years previously she developed severe myopathy. She was diagnosed with polymyositis and administered methylprednisolone 40 mg once a day (QD) and

cyclophosphamide 50 mg QD. She lapsed into intermittent coma due to hyperemic ammonia however, thus cyclophosphamide was discontinued, and methylprednisolone 20 mg QD was initiated and has been maintained to date.

Personal and family history

She had no family history of genetically related diseases, but her daughter had hepatitis C and had been treated with interferon.

Physical examination

Physical examination revealed no fever, heart rate 70 bpm, blood pressure 140/90 mmHg, O₂ saturation 94% on room air, second heart sound accentuation, and moderate edema in both lower limbs.

Laboratory examinations

Primary laboratory data on admission are shown in Table 1. The 6-minute walking distance was 100 m.

Imaging examinations

Muscle biopsy showed striated muscle atrophy with inflammatory cell infiltration (Figure 1A). Electrocardiography indicated a normal sinus rhythm (Figure 1B). Transthoracic echocardiography showed enlargement of the left atrium (43.7 × 45.2 × 60.0), right atrium (59.8 × 39.4), and right ventricle (49.3), normal LV ejection fraction (71.3%), elevated pulmonary artery pressure (61 mmHg), and reduced diastolic function (Figure 1C-F). Chest computed tomography (CT) depicted pulmonary arterial hypertension, right atrium and right ventricle enlargement, and no parenchymal lung disease (Figure 2A-C). Pulmonary ventilation/perfusion scanning indicated no evidence of typical signs of thromboembolic disease (Figure 2D). Abdominal CT suggested normal liver size with a hepato-renal shunt and a spleno-renal shunt (Figure 2E-F). Right heart catheterization showed that mPAP was 55.33, pulmonary artery

wedge pressure (PAWP) was 24, and pulmonary vascular resistance was 5.13 Woods units (WU) (Table 2).

FINAL DIAGNOSIS

Based on the medical history, symptoms, and auxiliary examinations, a diagnosis of moderate PH, nephrotic syndrome, polymyositis, hypertension, and hepatitis C was determined.

TREATMENT

The patient was treated with sildenafil 20 mg QD, macitentan 10 mg QD, irbesartan and hydrochlorothiazide 150 mg QD, furosemide 20 mg QD, and methylprednisolone 80 mg QD with the dose gradually reduced to 20 mg QD. Due to suspected hepatitis C-induced multiple organ injury the patient was referred to the gastroenterology department for further assessment of liver disease. There was no evidence of a liver tumor. Liver stiffness as evaluated by transient elastography was 8.3 kPa. Hepatitis C antibody was 6.8 S/CO, but serum tests were negative for HCV RNA. Therefore, she was not prescribed antiviral therapy.

OUTCOME AND FOLLOW-UP

At the 3-month follow up the patient's dyspnea was dramatically improved and the 6-minute walking distance was 300 m and pulmonary artery pressure drops to 50 mmHg.

DISCUSSION

HCV infection should be considered a systemic disease which is often associated with many extrahepatic manifestations. According to different studies, 40-80% of patients infected with HCV develop at least one extrahepatic manifestation^[4]. However, pulmonary hypertension associated with HCV is relatively rare.

⁴PH is divided into five clinical subgroups; pulmonary arterial hypertension (PAH), PH associated with left heart disease, PH associated with chronic lung disease and/or

hypoxia, chronic thromboembolic, and PH with unclear and/or multifactorial mechanisms. ⁸ Pre-capillary PH is hemodynamically defined as mPAP > 20 mmHg, PAWP ≤15 mmHg, and pulmonary vascular resistance (PVR) > 2 WU. PAWP >15 mmHg is the threshold of post-capillary PH. ³ PVR is used to distinguish patients with post-capillary PH who have significant components of pre-capillary PH (PVR > 2 WU, combined with post-capillary and pre-capillary PH; CpcPH) from those who do not (PVR ≤ 2 WU, isolated post-capillary PH) [5]. The current patient had no relevant family history to support a heritable cause of PH. Valvular/congenital heart diseases, lung diseases, chronic pulmonary artery obstruction, and human immunodeficiency virus infection were systemically eliminated *via* relevant tests. Drugs were also unlikely to have caused her PH. The onset of PH predated the polymyositis, and connective tissue disease could also be excluded as a cause of PH. Thus, the possibility remained that PH associated with portal hypertension was due to chronic hepatitis C.

Portal PH (PoPH) is a well-known serious complication of portal hypertension in chronic liver disease. According to statistics, PoPH occurs in 1%–2% of patients with liver disease and portal hypertension [6]. The incidence of PoPH is higher in patients with HCV-related cirrhosis. In PAH registry studies, PoPH patients accounted for 5%–15% of PAH patients [7–9]. Hemodynamically, patients with PoPH had significantly ¹³ higher cardiac output and lower systemic and pulmonary vascular resistance than ¹ patients with idiopathic PH [10]. The diagnosis of PoPH is based on the presence of otherwise unexplained pre-capillary PH in patients with portal hypertension or a portosystemic shunt ¹ [5]. In patients with an established diagnosis of PoPH, treatment should follow the same general principles as in other patients with PAH. PAH medications can affect gas exchange, which may deteriorate with vasodilators in patients with PoPH ¹ [11]. Various case series support the use of approved PAH ⁶ medication in patients with PoPH. The survival and prognostic factors in PoPH remain controversial and are still poorly studied in the current era of PH management [7, 12, 13]. The current patient had a history of hepatitis C virus infection, mild liver fibrosis, and hepato-renal shunt, thus the diagnosis of PoPH was considered. The results of right

heart catheterization in the present patient were consistent with CpcPH, considering that there may have been other factors involved in PH, not only PoPH. The patient had a history of hypertension with left atrium and right atrium enlargement, and the N-terminal-pro B-type natriuretic peptide was elevated. Therefore, heart failure with preserved ejection fraction was involved in PH. Sildenafil, macitentan, diuretics, and angiotensin receptor blocker were prescribed. Short-term follow-up indicated improvement in respiratory status and increased activity tolerance. Confirmation of further efficacy requires long-term follow-up.

What is intriguing in the current case is the coexistence of PH, nephrotic syndrome, and polymyositis in a chronic hepatitis C patient, which is reported herein for the first time to our knowledge. Increasing epidemiological evidence indicates an association between HCV infection and renal disease, with membranoproliferative glomerulonephritis and membranous nephropathy being the most common [14]. The main clinical manifestations of nephrotic syndrome in HCV-infected patients are proteinuria and hypoalbuminemia, with or without a reduced glomerular filtration rate. Treatments include antiviral and nonspecific immunosuppressive therapy [15], but their efficacy and safety are controversial. HCV infection is often associated with autoimmune diseases such as cryoglobulinemia, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, dermatomyositis, and polymyositis [1, 16-18]. Most of these diseases appear to be related to virus-induced non-specific activation of the immune system, including autoantibody production, cryoglobulinemia, autoimmune thyroid disorders, and B cell lymphomas [19]. Although most data are based on small series and case reports, the association between chronic HCV infection and systemic autoimmune disease has received increasing attention. The exact etiology is unknown, but interaction between viral infection and autoimmune responses is thought to be one of the mechanisms involved. Chronic HCV infection should be considered as the cause of polymyositis if no other etiology is found. The diagnosis and treatment of HCV-associated autoimmune features has become a clinical challenge in patients with HCV infection. There are few reports on the outcome of corticosteroid treatment in

patients with chronic HCV infection. Several studies have described rapid progression of liver disease after immunosuppression therapy in patients with chronic HCV infection^[20]. The current patient's nephrotic syndrome and polymyositis may have been caused by chronic HCV infection *via* an autoimmune mechanism. The patient was initially treated with methylprednisolone and cyclophosphamide at the time of her polymyositis diagnosis. However, cyclophosphamide was discontinued and methylprednisolone was reduced because of her repeated episodes of abnormal behavior and coma due to hyperammonemia.

The optimal treatment strategy for hepatitis C-related extrahepatic manifestations remains to be determined. Due to the limited data available, more information is needed before definitive therapeutic recommendations can be established. The guidelines for treatment of HCV-related extrahepatic manifestations should be based on clinical features rather than underlying pathogenic mechanisms. Because of the poor prognosis and high mortality associated with these manifestations, the establishment of a safe and effective regimen for the therapy of HCV-related extrahepatic features requires further investigation.

CONCLUSION

Herein we have described a case of chronic hepatitis C with coexisting PoPH, nephrotic syndrome, and polymyositis. Increasing evidence supports a relationship between hepatitis C infection and diverse extrahepatic manifestations, but it is very rare to have multiple different extrahepatic manifestations in a single patient. To our knowledge, this is the first reported case. The exact mechanism by which hepatitis C mediated the development of diverse extrahepatic manifestations remains unclear. Further research on the specific mechanism involved is needed, to facilitate the development of safer and more effective treatment plans.

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