Clinical Case Report

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# Pernicious anemia associated with cryptogenic cirrhosis

## Two case reports and a literature review

Xin Yan, MD, Runping Gao, PhD, Yulin Hu, PhD, Jinglan Jin, PhD*

**Abstract**

**Rationale:** Pernicious anemia (PA) is an autoimmune gastritis that results from the destruction of gastric parietal cells and the associated lack of an intrinsic factor to bind ingested vitamin B12. While an association between PA and various liver diseases has been rarely reported, reports of associated diseases include primary biliary cholangitis, autoimmune hepatitis, and Interferon-treated hepatitis C. We present 2 cases of PA associated with cryptogenic cirrhosis (CC), which has not been previously reported in the literature.

**Patient concerns:** A 42-year-old man presented with fatigue, pallor, and sustained abdominal distension that had persisted for 15 days. An 87-year-old man was admitted to the hospital for an unsteady gait and loss of appetite that had persisted for 20 days.

**Diagnoses:** Symptoms, laboratory tests, and imaging findings for both patients were indicative of PA and CC.Both had neurological and psychiatric symptoms during hospitalization that were ultimately linked to a vitamin B12 deficiency but not hepatic encephalopathy.

**Interventions:** Both patients received intramuscular injections of vitamin B12.

**Outcomes:** Hemoglobin levels of the 2 patients increased gradually, and their neurological symptoms were alleviated.

**Lessons:** PA associated with a liver disease is rare, and the underlying mechanism can only now be clarified. We speculate that autoimmune dysfunction and chronic vitamin B12 deficiency caused by PA might be unique causes of liver cirrhosis. Additional investigations are needed to verify these findings.

**Abbreviations:** AIG = autoimmune gastritis, AIH = autoimmune hepatitis, CC = cryptogenic cirrhosis, CT = computed tomography, HE = hepatic encephalopathy, IFA = intrinsic factor antibody, MRI = magnetic resonance imaging, NASH = non-alcoholic steatohepatitis, PA = pernicious anemia, PBC = primary biliary cholangitis, PCA = parietal cell antibody, SAM = S-adenosylmethionine.

**Keywords:** autoimmune gastritis, cryptogenic cirrhosis, hepatic encephalopathy, pernicious anemia, vitamin B12 deficiency

## 1. Introduction

Pernicious anemia (PA) is an autoimmune gastritis (AIG) that results from the destruction of gastric parietal cells and the associated lack of an intrinsic factor to bind ingested vitamin $B_{12}$.[1] The association between PA and liver diseases, although rare, has been documented for various liver diseases including primary biliary cholangitis (PBC),[2–8] autoimmune hepatitis (AIH),[9,10] and Interferon-treated hepatitis C.[11–15] Moreover, vitamin $B_{12}$ deficiency presents mainly with neurological and psychiatric manifestations,[16] which are easily confused with those of hepatic encephalopathy (HE). We present 2 cases of PA associated with cryptogenic cirrhosis (CC), which has been not previously reported in the literature. Initial diagnosis at admission was HE for both cases, which was later changed to chronic vitamin $B_{12}$ deficiency after consideration of the neuropsychiatric symptoms.

This case report was approved by the ethics committee of the First Hospital of Jilin University, Changchun, China. Informed consent was obtained from the patients for the publication of this case report.

## 2. Case report

### 2.1. Case 1

A 42-year-old man presented with fatigue, pallor, and sustained abdominal distension that had persisted for 15 days. On physical examination, he had a severe pale appearance, tremor, and limb weakness. His gait was unsteady and stiff, and he was unable to run or walk straight. Laboratory tests revealed a negative serology for hepatitis A, B, C, and E, a hemoglobin level of 60 g/L (normal range, 130–150 g/L), a mean corpuscular volume (MCV) of 121 fL (normal range, 82–100 fL), and a serum vitamin $B_{12}$ level of 14 pmol/L (normal range, 133–675 pmol/L). Folate levels and an iron metabolism test were both normal. He had detectable levels of both parietal cell antibody (PCA) and intrinsic factor antibody (IFA). The major laboratory test results are shown in Table 1, which include an abnormal liver function test, a routine

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Department of Hepatology, The First Hospital of Jilin University, Jilin University, Changchun, Jilin, China.

* Correspondence: Jinglan Jin, Department of Hepatology, The First Hospital of Jilin University, Jilin University, No. 71, Xinmin Street, Changchun, Jilin, 130021, China (e-mail: jinjinglan197896@163.com).



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**Table 1**

**Laboratory investigations.**

| Investigation | Case 1 | Case 2 | Normal range |
|---|---|---|---|
| Hemoglobin, g/L | 67 | 60 | 130–175 |
| WBC count, $\times 10^9$/L | 3.5 | 2.49 | 3.5–9.5 |
| MCV, fL | 125.7 | 121 | 82–100 |
| MCH, pg | 44.1 | 43.5 | 27–34 |
| Platelet, $\times 10^9$/L | 50 | 33 | 125–350 |
| PT, s | 15.5 | 128 | 9–13 |
| INR | 1.31 | 1.09 | 0.8–1.2 |
| AST, U/L | 60.5 | 55.4 | 15–40 |
| ALT, U/L | 20.4 | 31.5 | 9–50 |
| Total bilirubin, μmol/L | 23.4 | 51.1f | 6.8–30.0 |
| Albumin, g/L | 28.2 | 38 | 40–55 |
| Folic acid, ng/mL | 3.95 | 6.68 | 3.1–19.9 |
| Vitamin B12, pmol/L | 47 | 14 | 133–675 |
| Homocysteine, μmol/L | 38 | 50 | 0–20 |
| PCA | + | + | − |
| IFA | + | + | − |
| Other autoantibodies | − | − | − |

ALT = alanine aminotransferase, AST = aspartate aminotransferase, IFA = intrinsic factor antibody, INR = international normalized ratio, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, PCA = parietal cell antibody, PT = plasma prothrombin time, WBC = white blood cell.

blood test, and a coagulation test. An abdominal computed tomography (CT; Fig. 1) showed evidence of liver cirrhosis, splenomegaly, ascites, and portal hypertension. The patient was subjected to brain magnetic resonance imaging, which showed symmetrical, high-intensity signal in the pallidum on T1- and T2-weighted images (Fig. 2A and B). The neuroimaging diagnosis was metabolic encephalopathy. An examination of the bone marrow indicated megaloblastic anemia, and a peripheral blood smear showed macrocytes and reduced platelet counts. No hematemesis, clay-colored stool, or fever was reported. His medical history was unremarkable. There was no history of alcohol or drug abuse, blood transfusions, or liver disease. After admission, he was given glutathione and treated for his symptoms.

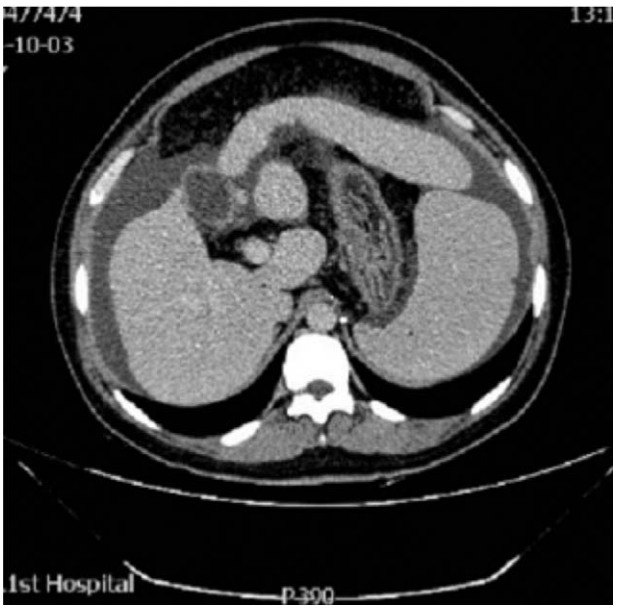


**Figure 1.** An abdominal computed tomography image shows a small liver with a rough surface, different sizes of hepatic lobules, a wide hepatic hiatus, and a large spleen. Fluid is visible around the liver and spleen. The diameter of the main portal vein is 15 mm.

On the fifth day after admission, the patient appeared lethargic and could not be aroused from sleep, but he had orbital pressure reflection, a corneal reflex, and a pupillary light reflex. Pathological signs were not evident. Blood ammonia levels were slightly increased (62 μmol/L, normal range, 9–47 μmol/L). After considering the imaging diagnosis with liver cirrhosis and lack of consciousness, a diagnosis of HE was made. The patient immediately received treatment for a hepatic coma. He recovered consciousness gradually. However, since then, the patient has exhibited tremor, muscular hypertonia, and an unsteady gait. Peripheral blood levels of hemoglobin decreased significantly on the fifth day after admission (47 g/L). An endoscopy revealed mild esophageal and gastric varices, indicative of chronic atrophic gastritis. A liver biopsy revealed chronic liver injury, interlobular bile duct hyperplasia, and stenosis, with a histological stage of G1S3 (METAVIR score; Fig. 3).[17]

With a diagnosis of PA, the patient received an intramuscular injection of 500 μg vitamin $B_{12}$ daily for the first 14 days, then weekly for 4 weeks over a long-term period. With such treatment, the patient's hemoglobin levels increased gradually, and the neurological symptoms were alleviated. After 1 year of treatment, the patient's hemoglobin level was 156 g/L. Due to cirrhosis and esophageal varices, the patient died of gastrointestinal bleeding 2 years later.

### 2.2. Case 2

An 87-year-old man was admitted to the hospital due to an unsteady gait and loss of appetite that had persisted for 20 days. On admission, the patient looked drowsy and pale; moreover, he was delusional and had sleep disturbances.

Laboratory tests revealed a negative serology for hepatitis A, B, C, and E, a hemoglobin level of 67 g/L, an MCV of 125.7 fL, and a serum vitamin $B_{12}$ level of 47 pmol/L. Folate levels and an iron metabolism test were normal. The blood ammonia level was 80 μmol/L. He had detectable levels of both PCA and IFA. The major laboratory test results are shown in Table 1. An abdominal CT with contrast revealed liver cirrhosis and ascites, and an examination of the bone marrow revealed megaloblastic anemia. A liver biopsy was not performed.

On the second day after admission, liver cirrhosis, HE, and severe anemia were diagnosed. After considering the imaging diagnosis with liver cirrhosis and his neurological performance, a diagnosis of HE was made. Even though repeated red blood cell transfusions and treatment for hepatic coma were administered, anemia and awareness were not significantly improved. The patient received an intramuscular injection of 500 μg vitamin $B_{12}$ daily. After 7 days of treatment, the anemia, appetite, and delusion gradually improved.

After 1 year of treatment, the hemoglobin level of the patient was 108 g/L. Continued follow-up for 3 years until May 11st, 2018 revealed no recurrence of neuropsychiatric symptoms or anemia.

## 3. Discussion and conclusion

PA is an AIG that results from the destruction of gastric parietal cells and the associated lack of an intrinsic factor to bind ingested vitamin $B_{12}$. Severe vitamin $B_{12}$ deficiency can lead to macrocytic anemia and neurological symptoms, such as symmetric paresthesia, numbness, and gait problems.[1] The

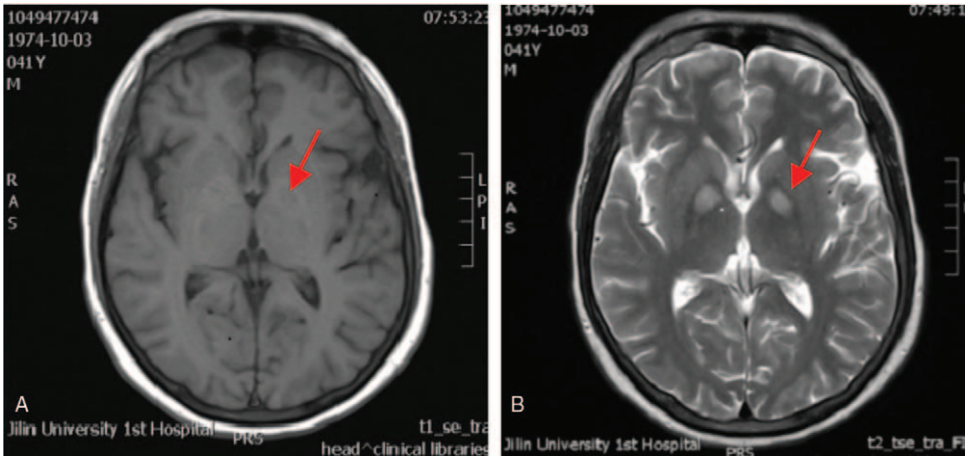


**Figure 2.** Brain magnetic resonance imaging shows symmetrical pallidum with high signal intensity on the (A) T1- and (B) T2-weighted images.

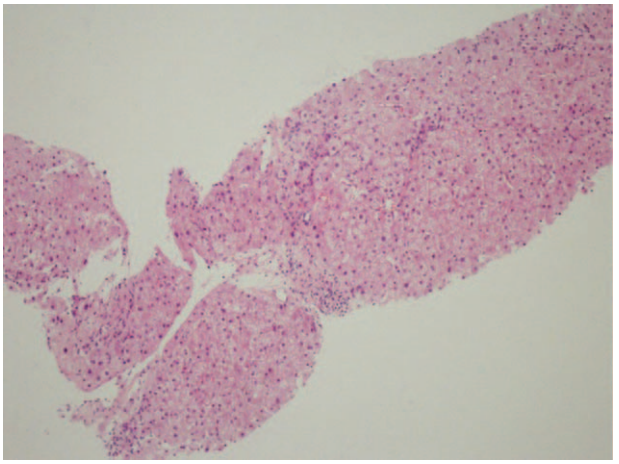

**Figure 3.** A liver biopsy revealed chronic liver injury, interlobular bile duct hyperplasia, and stenosis.

association of PA with autoimmune diseases, such as autoimmune thyroiditis, autoimmune diabetes, Sjögren syndrome, and vitiligo, is common.[18] There are few reports of an association between PA and various liver diseases; a review of liver diseases associated with PA reported in the literature is presented in Table 2. Of these documented 18 cases, 8 cases were PA combined with PBC, accounting for the largest number (44.4%), and all were women.[2–8] Five cases were hepatitis C after interferon therapy,[11–15] and the cause of the PA was thought to be due to the administration of interferon. Two cases were PA associated with AIH,[9,10] and both were combined with other autoimmune diseases, such as type 1 diabetes and atrophic thyroiditis. Two cases were PA with hepatitis C without interferon treatment. Only 1 case was PA associated with hepatitis B. In addition, we found that not all patients with PA and a liver disease had detectable levels of PCA and IFA. Many patients tested positive for the presence of other antibodies, including hepatitis B antibodies, hepatitis C antibodies, antinuclear antibodies, anti-mitochondrial antibodies, and anti-transglutaminase antibodies.

CC is a diagnosis of exclusion when there is no other known identifiable etiology[19]; various descriptions of the etiology of CC have been postulated, such as a history of hidden drinking, unknown viruses (not hepatitis B or C), phenotypic alpha-1 antitrypsin abnormalities, silent autoimmune hepatitis, or the development of NASH; it is important to note that a specific liver pathology may not always be clearly diagnosed.[20,21]

The 2 cases described here are concomitant PA with CC. We suspect that PA was the cause of the cirrhosis. Considering that PA is the final stage of AIG, which leads to the loss of parietal cells in the fundus and body of the stomach, the cause of liver cirrhosis in these cases is suspected to be autoimmune in origin. Liaskos et al[22] reported that patients with PBC often have detectable levels of PCA and IFA. In addition, severe and extensive gastric mucosal atrophy can occur in PBC patients.[23] A T cell-mediated mechanism may be important for the development of AIG.[24] Weng et al[25] found that crosstalk between T cells and type II NKT cells led to chronic autoimmune liver disease. PBC may be characterized by immunoregulatory disorders and a lack of tolerance to histocompatibility antigen-expressing tissues. Impairment of biliary epithelial cells rich in HLA class II antigens can lead to PBC.[26] Interestingly, HLA class II antigens have been observed in parietal cells in mice with PA.[4]

Additionally, a deficiency in vitamin $B_{12}$ caused by PA may also cause liver cirrhosis. On one hand, a lack of vitamin $B_{12}$ blocks the synthesis of S-adenosylmethionine (SAM), which results in the production of methionine synthase. However, SAM is the main cellular antioxidant in the liver, and a lack of SAM may cause liver damage and differentiation.[27,28] On the other hand, a vitamin $B_{12}$ and folate imbalance induces NK cytotoxicity and lymphocyte hyperplasia, which affect the immune system and may lead to liver injury.[29] Regardless of the cause of vitamin $B_{12}$ deficiency, it takes 1 or 2 decades for symptoms to occur. Even in asymptomatic patients, the effects of vitamin $B_{12}$ deficiency are not only profound but variable. Vitamin $B_{12}$ deficiency that is not associated with a hematological complication is often ignored. Autoimmune dysfunction and chronic vitamin $B_{12}$ deficiency might lead to decreased hepatic detoxification and damage repair, and to progression of chronic liver disease, like liver cirrhosis. At the same time, the 2 cases described above both show symptoms of confusion, unawareness, and unstable gait, which could easily be misdiagnosed as HE. If the treatment for

**Table 2**

**Review of liver diseases associated with PA reported in the literature.**

| Reference | Sex | Age | Citizenship | PCA | IFA | Other antibodies | Liver diseases | Other disease |
|---|---|---|---|---|---|---|---|---|
| Jazia et al[2] | F | 68 | Tunisia. | – | – | AMA | PBC | N |
| Chung et al[3] | F | 46 | Canada | + | NR | ANA AMA | PBC | N |
| Aoyama et al[4] | F | 64 | Japan | + | + | AMA | PBC | N |
| Takahashi et al[5] | F | 52 | Japan | – | + | antipyruvate dehydrogenase complex antibody | PBC | N |
| Dohmen et al[6] | F | 72 | Japan | NR | NR | NR | PBC | N |
| Arikan et al [7] | F | 54 | Turkei | NR | NR | NR | PBC | NR |
| Renoux et al [8] | F | 68 | France | NR | NR | NR | PBC | N |
| Renoux et al [8] | F | 46 | France | NR | NR | NR | PBC | N |
| Bergwitz et al[9] | M | 60 | America | – | – | NR | AIH | Addison disease, atrophic thyroiditis |
| De Block et al[10] | F | 45 | Belgium. | + | + | ANA | AIH | Type1 diabetes |
| Ichihara et al[11] | M | 62 | Japan | NR | NR | HCV-Ab | HCV-IFN | N |
| Andres et al[12] | F | 52 | France | + | + | NR | HBV | N |
| Andres et al [12] | M | 45 | France | + | + | HCV-Ab | HCV-IFN | N |
| Andres et al [12] | M | 82 | France | – | + | HCV-Ab ANA | HCV | N |
| Andres et al [12] | M | 38 | France | – | + | HCV-Ab antitransglutaminase antibody | HCV | N |
| Musialik et al[13] | M | 46 | Poland | – | + | HCV-Ab ANA | HCV-IFN-ribavirin | N |
| Borgia et al [14] | M | 61 | Italy | – | – | HCV-Ab | HCV-IFN | N |
| Willson[15] | F | 54 | America | – | + | ANA | HCV-IFN | N |

AIH = autoimmune hepatitis, AMA = antimitochondrial antibody, ANA = anti-nuclear antibody, HCV-IFN = Interferon-treated Hepatitis C, N = none, NR = not reported, PA = pernicious anemia, PBC = primary biliary cirrhosis.

HE had no effect, we should have suspected that lack of vitamin $B_{12}$ could cause the neurological symptoms. Vitamin $B_{12}$ could be easily administered in a timely manner.

We presented 2 cases of PA associated with CC. Currently, no similar reports have been published. These 2 cases illustrate the possible association between PA and CC, and further investigations are needed to clarify the pathogenesis of PA associated with CC. As mild anemia is usually asymptomatic and easily overlooked, clinicians should keep in mind the possible association of PA and PBC. In cases of severe vitamin $B_{12}$ deficiency, patients may present with neurological and psychiatric symptoms,[16] which are easily confused with those of HE; attention should thus be paid to the identification of a vitamin deficiency and its timely supplementation.

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## Author contributions

**Formal analysis:** Runping Gao, Yulin Hu.
**Writing – original draft:** Xin Yan, Jinglan Jin.
**Writing – review & editing:** Xin Yan, Jinglan Jin.

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