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Pernicious Anemia in Patients with Primary Biliary Cirrhosis, Autoimmune Hepatitis, and Chronic Viral Hepatitis

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Abstract

Backgrounds: Cases of Pernicious Anemia (PA) with Autoimmune Liver Diseases (ALDs) or chronic viral hepatitis have been uncommon. There have been few articles regarding the associations between these diseases.

Methods: A review of concomitant cases of PA in patients with ALDs, such as Auto Immune Hepatitis (AIH) or Primary Biliary Cirrhosis (PBC), and patients with chronic viral hepatitis with or without Interferon (IFN) treatment were conducted.

Results: Six cases of concomitant PA and ALDs (five were PBC and one was AIH) and seven cases of chronic viral hepatitis (six were due to HCV, one was due to HBV; five cases were of IFN-induced PA and two were of PA without IFN treatment) have been reported. In these concomitant cases, serum vitamin B_{12} deficiency was documented in all 13 cases and serum Intrinsic Factor Antibodies (IFA) were positive in 11 of 12 cases, excluding one case in which detection of IFA was not mentioned.

Conclusions: Although concomitant cases of PA in patients with ALDs or chronic viral hepatitis have been rarely reported, PA should be considered in cases of progressive macrocytic anemia in these patients.

Keywords: Autoimmune liver diseases; Primary biliary cirrhosis; Pernicious anemia; Interferon; Intrinsic factor antibodies

Introduction

Autoimmune Liver Diseases (ALDs) include Auto Immune Hepatitis (AIH), Primary Biliary Cirrhosis (PBC), and Primary Sclerosing Cholangitis (PSC). Pernicious Anemia (PA) involves an autoimmune process in which atrophy of the gastric mucosa reduces the production of Intrinsic Factor (IF) via parietal cells, inducing vitamin B_{12} deficiency and megaloblastic anemia [1-5]. Although autoimmune diseases often coexist in patients, cases of concomitant PA and ALD are rarely reported. Moreover, Interferon (IFN) treatment may rarely induce PA in patients with viral hepatitis [6-11].

Thus far, there have been few reports of these associations, and the clinical features and related mechanisms are not completely understood. Here, concomitant cases of PA in patients with ALD and cases of chronic viral hepatitis during IFN treatments or without IFN treatments, as reported in the English and Japanese scientific literature, are reviewed and summarized.

Methods

A review of the English and Japanese literature regarding concomitant PA in patients with ALD and patients with chronic viral hepatitis with IFN-induced PA or without IFN treatments was conducted and the findings in such reports published since 1980 was summarized. The English and Japanese literature was reviewed using PubMed and Japana Centra Revuo Medicina (Igaku Chuo Zasshi), respectively. A literature search was performed using the following keyword combinations: (1) pernicious anemia and autoimmune liver disease, (2) pernicious anemia and autoimmune hepatitis, (3) pernicious anemia and primary biliary cirrhosis, (4) pernicious anemia and primary sclerosing cholangitis, (5) pernicious anemia and chronic viral hepatitis, and (6) pernicious anemia and interferon. In reported concomitant cases of PA and liver diseases, diagnoses of PA [1], PBC [12], and AIH [13] were conducted according to the diagnostic criteria of the disease (described later).

Pernicious Anemia

PA is a disease of complex autoimmune origin and is caused by the impaired absorption of vitamin B_{12} due to the absence of IF, thus inducing megaloblastic anemia [1-5]. PA is relatively common in humans older than 60 years and is the most common cause of vitamin B_{12} deficiency and megaloblastic anemia [2-5]. The autoimmune origin of PA is supported by the presence of autoantibodies for gastric parietal cells and/or IF [4]. PA is diagnosed according to the following diagnostic criteria: 1) megaloblastic anemia [high mean corpuscular volume (≥120 fL) of red blood cells], 2) low levels of serum vitamin B_{12}, 3) gastric body mucosal atrophy, and 4) presence of autoantibodies for gastric parietal cells and/or IF [1].

The gastric enzyme H^+/K^+-ATPase (proton pump) is the target antigen recognized by gastric parietal cell antibodies (PCA) [1]. PCA bind to gastric H^+/K^+-ATPase, which is responsible for acid secretion in the stomach, and lead to the destruction of the IF-producing parietal cells in the stomach [14]. IF antibodies (IFA) can bind to the vitamin B_{12} binding site on the IF molecule (type 1), or bind elsewhere and prevent binding of IF to the ileal mucosa (type 2), thus preventing the absorption of IF–vitamin B_{12} complex [5,14].

The prevalence of gastric PCA and IFA in patients with PA is

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approximately 80%–90% and 40%–70%, respectively [1,2,5,15,16]. However, PCA can be detected in other autoimmune diseases, such as autoimmune thyroid diseases [i.e., Hashimoto's thyroiditis (HT)], Addison's disease, and type I Diabetes Mellitus (DM), all of which are well documented as PA-associated autoimmune diseases [5,16,17]. Moreover, the incidence of PCA decreases due to the progression of autoimmune gastritis or at a later stage of PA [3,5]. Therefore, the detection of PCA may not be specific for PA [5,16]. In contrast, IFA detection may be useful for diagnosing PA and autoimmune gastritis [14] because, unlike PCA, the incidence of IFA seems to increase to 60%–80% with the prolonged duration of disease [5]. Therefore, IFA may be relatively specific for PA compared with the detection of PCA [16]. Treatment for PA is generally the non-oral administration of vitamin B_{12}, and an increase in the reticulocyte count is used as a sign of a hematological response to therapy [4].

PCA or IFA in patients with liver diseases

Although there have been few reports regarding the incidence of PCA or IFA positivity in several liver diseases, Liaskos et al. [2] reported a significantly higher IgG-PCA detection frequency in the cases of PBC (50/157; 31.8%) compared with the cases of other liver diseases, such as AIH, PSC, viral hepatitis, alcoholic liver disease, and nonalcoholic steatohepatitis (total prevalence of liver diseases excluding PBC: 26/261; 10%), and compared with healthy controls (10/96; 10.4%). The same study reported an IgG-IFA prevalence of 3.8% (6/157) in patients with PBC (all six patients were also PCA-positive). IgG-IFA was not detected in patients with other liver diseases (0/261) or healthy controls (0/96) irrespective of the presence of PCA [2].

PBC and extrahepatic manifestations

PBC is a chronic immune-mediated disease of unknown etiology, although genetic associations and environmental factors may affect individual host susceptibility [18]. This disorder manifests itself as an organ-specific disturbance characterized by progressive cholestasis with interlobular bile duct destruction and predominantly affects middle-aged females [19]. PBC also characteristically features the presence of anti-mitochondrial autoantibodies or pathological findings, and the diagnosis of PBC is established if two of the three objective criteria are present: 1) elevated serum alkaline phosphatase; 2) presence of antimitochondrial antibody, which is useful for the serological diagnosis of PBC; and 3) liver histology findings (presence of chronic, non-suppurative, destructive cholangitis) [12]. One common extrahepatic autoimmune manifestation observed in PBC patients is Sjögren's syndrome [20]. Other frequent extrahepatic autoimmune manifestations include HT and Raynaud's syndrome, systemic sclerosis, rheumatoid arthritis, and type I DM [20,21].

Clinical characteristics of concomitant PBC and PA

Culp et al. [22] reported a PBC and PA coexistence rate of 1.8% (2/113) and noted that PA was diagnosed prior to the development of PBC in concomitant cases. However, age, gender, and clinical features in two cases were not mentioned. The cases of concomitant PBC and PA are rarely reported; to the best of our knowledge, only five cases have been reported in the English and Japanese scientific literature [3,15-17,23], excluding the two cases reported by Culp et al. [22]. All five of these patients were females. PBC was first diagnosed in two cases [15,23], and both diseases, PBC and PA, were diagnosed almost simultaneously in the remaining three cases [3,15,16]. The age of the patients at the time of diagnosis of both diseases ranged from 46 to 72 years, and the interval between the diagnoses of the primary and concomitant diseases ranged from 0 to 19 years. Serum vitamin B_{12} deficiency was found in all five cases. Serum IFA was positive in three cases [15,16,23], negative in one case [3], and unclear in one case [17]. Serum PCA was positive in three cases [16,17,23] and negative in the remaining two cases [3,15]. Concomitant cases of PA and cases of PA without liver disease were treated with vitamin B_{12} injections, and recovery after treatment occurred in all five cases. In patients who underwent liver biopsy, the pathological findings of PBC varied from stage I to *II* according to the Scheuer classification, and no cirrhosis cases were found. Ursodeoxycholic acid was the standard pharmacotherapy for patients with PA and PBC in the reports, although liver transplantation was performed in one case [17]. No reported cases of concomitant PA and PBC were fatal.

PA in patients with AIH or PSC

AIH is characterized by female predilection and diagnosed by the following findings: 1) elevated aminotransferases; 2) non-species or organ-specific autoantibodies; 3) increased levels of γ-globulin or immunoglobulin (Ig) G and 4) histological findings such as interface hepatitis on liver biopsy [13]. AIH can be divided into two sub-types (type 1 and type 2) type 1 AIH is characterized by the presence of anti-nuclear antibodies and/or anti-smooth muscle antibodies, whereas type 2 AIH is characterized by anti-liver/kidney microsome type 1 antibodies and/or anti-liver cytosol type 1 antibodies [24]. Approximately 20%–30% of type 2 AIH patients show other autoimmune diseases, such as type 1 DM, autoimmune thyroid diseases, and Addison's disease [25], all of which are well documented as PA-associated autoimmune diseases [16]. However, there have been few case reports of concomitant PA in AIH patients. To the best of our knowledge, only one report of PA in patients with AIH is available; De Block et al. [25] reported a case of a man with type 2 AIH and type 1 DM who developed PA with serum vitamin B_{12} deficiency and serological positive PCA and IFA. PSC is a cholestatic liver disease associated with autoimmune processes, although there are many clinical and epidemiological differences between PBC and PSC. PSC is best known for its hepatobiliary manifestations accompanied by ulcerative colitis. However, to the best of our knowledge, no reports of PA in patients with PSC are available.

PA in patients with viral hepatitis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the main causes of chronic liver diseases and hepatocellular carcinoma world-wide. Case reports of PA in patients with chronic hepatitis B or hepatitis C without IFN treatment have rarely been reported; Andrès et al. [6,7] reported two cases with chronic viral hepatitis due to HBV (one case) and HCV (one case). Serum vitamin B_{12} deficiency and serum IFA positivity were found in both cases [6,7]. Cases of IFN-induced PA in patients with chronic hepatitis due to HCV are sporadically documented. IFN has immunomodulatory properties, and the development of autoimmune phenomena during prolonged therapies is recognized [10]. Moreover, IFN induces production of organ-specific or nonspecific antibodies in more than half of the patients [11].

To the best of our knowledge, only five cases of chronic hepatitis due to HCV have been reported in the English and Japanese scientific literature [6-11]. The age of the patients ranged from 45 to 62 years, and there were three males and two females. The varieties of IFN administered were IFN-α for three cases [6,7,9,10], IFN-β for one case [8], and pegylated IFN plus ribavirin for one case [11]. The duration of IFN administration until the development of PA was 2–29 months. Serum vitamin B_{12} deficiency was found in all five cases. Serum IFA was positive in all cases. Serum PCA was positive in one case [8], negative in two cases [9,10], and unclear in two cases [6,7,11]. Concomitant cases

of PA were treated with vitamin B_{12} injections. Three cases recovered following treatment [8,9,11] and the outcomes for two cases were unclear [6,7,10]. No cases were fatal.

Although IFN treatment often induces hematological disorders and the development of PA during IFN treatment is rare, PA should be considered in cases of progressive macrocytic anemia (high mean corpuscular volume) or pancytopenia or progressive hematological disorders even after IFN treatment is discontinued.

Conclusions

This article has reviewed and summarized concomitant six cases of concomitant PA and ALDs (five were PBC and one was AIH) and seven cases of chronic viral hepatitis (six were due to HCV, one was due to HBV; five cases of IFN-induced PA and two were of PA without IFN treatment). PA should be considered in the cases of progressive macrocytic anemia, particularly in patients with PBC or chronic viral hepatitis during or after IFN treatment. Serum vitamin B_{12} deficiency and detection of serum IFA or PCA seems to be significant for diagnosis of concomitant PA.

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