



Letter to the Editor

Primary sclerosing cholangitis in common variable immune deficiency



Dear Editor

Common variable immune deficiency (CVID) is the most common primary immune deficiency in adults and children, and is characterized by reduced or absent antibody production along with reduced serum levels of immunoglobulins, IgG, IgA, and/or IgM.¹ The main manifestation of this disease is recurrent infections. However CVID is known to have a heterogeneous phenotype² and is associated with multiple autoimmune conditions such as hemolytic anemia, immune thrombocytopenic purpura, rheumatoid arthritis, systemic lupus, inflammatory bowel disease (IBD) and also multiple autoimmune liver conditions.^{2,3} The most commonly reported liver diseases in CVID include viral hepatitis, nodular regenerative hyperplasia (NRH), primary biliary cirrhosis and autoimmune hepatitis.^{3–5} Primary sclerosing cholangitis (PSC) is another form of autoimmune liver disease with a heterogeneous presentation characterized by chronic inflammation of the biliary epithelium resulting in chronic cholestasis and multifocal bile duct strictures.⁶ This disease can affect the entire biliary tree and lead to fibrosis of the hepatic parenchyma and biliary system, ending in cirrhosis and malignancy.⁷

Herein we report two cases of PSC associated with CVID. To our knowledge, this is the first report of such association in literature.

Case 1

The first case is a 66-year-old male who had been in good state of health until age 45 when he developed diarrhea and was diagnosed with Ulcerative Colitis (UC) after a colonoscopy with biopsies at another hospital. His UC remained quiescent on oral 5-ASA. At age 50, he developed pruritus and elevated liver enzymes. Viral hepatitis markers were all reported negatives. After a complete work up including imaging, Endoscopic Retrograde Cholangiopancreatography (ERCP) (Fig. 1) and liver biopsy, he was diagnosed with PSC. PSC progressed over the course of 4 years and the patient underwent successful liver transplant for end stage liver disease. Additionally the patient had history of recurrent urinary tract infections, *C. difficile* colitis, basal cell carcinoma on face, and skin melanomas on scalp and thigh. His UC was under control for almost 10 years until he developed persistent diarrhea. He underwent colonoscopy and biopsy that were reported with no pathological changes. No improvement in diarrhea was achieved by changing his transplant medication including discontinuation of the sirolimus. Of note, patient experienced two episodes of

pneumonia requiring hospitalization at ages 61 and 65. His immune work up at that time showed low immunoglobulin titers; IgG of 276 mg/dL (normal range 694–1618 mg/dL), IgA 45 mg/dL (normal range 81–463 mg/dL), and IgM <5 mg/dL (normal range 48–271 mg/dL). He was referred to Northwestern immunology clinic for work up at this stage. We could trace back most of his past laboratory work up and could find another set of Immunoglobulin titers checked one year prior to the liver transplant that showed hypogammaglobulinemia of IgG 467 mg/dL, IgA 72 mg/dL and IgM <17 mg/dL. An infection cause could not be found despite extensive work up for chronic diarrhea. Immunologic studies showed no response to vaccination against pneumococcal disease. Further investigation for hypogammaglobulinemia including protein-losing syndromes was negative; subsequently patient was diagnosed with CVID. He was found to have diffuse bronchiectasis on high resolution CT scan of lungs. Patient was placed on monthly injections of Intravenous immunoglobulin (IVIG) at that point, and no infections have been reported in 1.5 year follow up.

Case 2

The second case is a 29-year-old female who had recurrent sino-pulmonary infections since childhood. At age 11, she was found to have bronchiectasis in the setting of recurrent lung infections and eventually at age 15 was diagnosed with CVID and was placed on IVIG. She continued to have multiple episodes of sinus infections, giardia infections and urinary tract infections. She was hospitalized for pneumonia several times, and also needed sinus surgery for recurrent pansinusitis unresponsive to chronic medical therapy. She had no response to pneumococcal vaccination. Like our first case, she developed pruritus and fatigue but at a younger age of 25. Her liver enzymes were elevated with alkaline phosphatase of 1820 mg/dL, ALT of 119 units/L, AST of 81 units/L and total bilirubin of 3.4 mg/dL. She had a complete work up and was diagnosed with PSC by Magnetic Resonance Cholangiopancreatogram (MRCP) and liver biopsy. Repeat MRCP in following years showed progression of PSC and her pruritus continued. Due to the extensive lung damage including diffuse bronchial wall thickening, bronchiectasis and bronchiolectasis throughout both lungs she could not tolerate a liver transplant surgery and is currently under evaluation for double lung/liver transplant.

Liver diseases are reported in a significant percentage of patients with CVID. In one study 12% of cases with CVID had evidence of liver disease.³ These abnormalities have been attributed to a broad spectrum of diseases. In past, the most common cause of hepatitis

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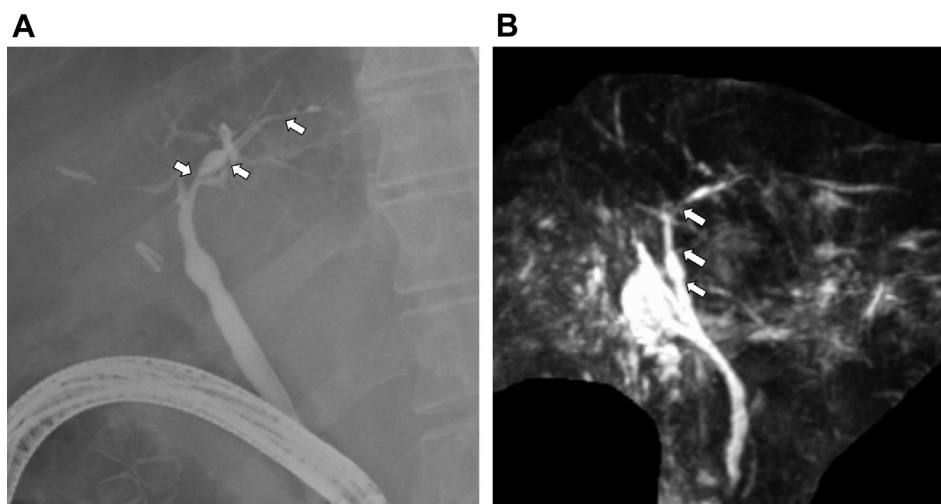


Fig. 1. A: ERCP picture of Case 1 showing localized areas of dilatation proximal to biliary strictures (arrows) indicative of PSC. B: MRCP image of Case 1 showing multiple strictures (arrows) followed by dilatation in intrahepatic ducts indicative of PSC.

in CVID was hepatitis C most probably due to contaminated immunoglobulin infusions.⁴ Another commonly reported liver disease in CVID that has been described more recently is nodular regenerative hyperplasia, which in some cases was associated with autoimmune hepatitis like disease.^{5,8} Furthermore some other forms of autoimmune liver diseases including primary biliary cirrhosis and autoimmune hepatitis have been reported in CVID.³ However we could not find any previous report of PSC in patients with CVID in the literature.

In case one the patient also suffers from UC. Inflammatory bowel disease (IBD), in particular UC is long known to be associated with PSC, and is reported in about two third of patients with PSC.⁹ On the other hand, the intestinal pathologies are fairly common in CVID patients and range from inflammatory bowel-like disease to sprue-like lesions of the small intestine leading to diarrhea.¹⁰ The only curative treatment for complicated PSC is liver transplant.⁶ This, however, in CVID patients could be limited by severely compromised lung function in the setting of extensive bronchiectasis. Thus, in CVID patients, earlier diagnosis of PSC and timely liver transplantation before progression of any ensuing lung damage should be taken into consideration.

Aside from cirrhosis and liver failure, PSC is strongly associated with cholangiocarcinoma, and also colon cancer in presence of concomitant IBD.⁶ These patients need to undergo immediate screenings at diagnosis (Ultrasonography, ERCP and colonoscopy) followed by an annual surveillance program to detect any evidence of the aforementioned malignancies at earlier stages. Therefore early diagnosis of PSC is crucial to start prompt implementation of cancer screening. This is even more clinically relevant in patients with CVID who are already at higher risk of cancer in general¹¹ and gastrointestinal malignancies in particular.^{12–14} This is important in the view of frequently reported gastrointestinal symptoms by CVID patients that could mask the early manifestations of GI cancers.¹⁵

We report two cases of primary sclerosing cholangitis in patients with CVID. The diagnosis of PSC should be considered when taking care of CVID patients who have evidence of liver disease. Early detection of PSC in CVID will help in timely implementation of liver transplantation prior to any potential lung sequel associated with CVID, and employment of cancer screenings and surveillances for the associated malignancies, leading to an overall better outcome of the patient.

Conflict of interest

The authors have no conflict of interest to declare.

Mahboobeh Mahdavinia^a, Mehdi Mirsaeidi^b, Faraz Bishehsari^c, Kris McGrath^{a,*}

^a Allergy/Immunology Division, Department of Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

^b Division of Pulmonary and Critical Care, Department of Medicine M/C 719, University of Illinois at Chicago, Chicago, IL, USA

^c Gastroenterology Division, Department of Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

* Corresponding author: Allergy/Immunology Division, Department of Medicine, Northwestern University, Feinberg School of Medicine, 676 N St Clair, Suite 1400, Chicago, IL 60611, USA.

E-mail address: k-mcgrath@northwestern.edu (K. McGrath).

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