Common Variable Immunodeficiency Presenting with Recurrent Ascending Cholangitis Treated with Oral Immunoglobulins

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Abstract:
Background: Common variable immunodeficiency (CVID) is a heterogeneous group of primary immune deficiency disorders that may be characterized by heightened susceptibility to gastrointestinal (GI) infection. GI conditions manifest in 20 to 50% of CVID patients but rarely include cholangitis.

Methods/Results: This is a 61-year-old female, with a history of cholecystectomy and gastric bypass, who presented with recurrent ascending cholangitis for eight years. After a hepaticojunostomy to correct a bile duct stricture complication from the cholecystectomy, ascending cholangitis was diagnosed by clinical presentation of fever and right upper quadrant pain and imaging revealing pneumobilia. CVID was diagnosed after no response to pneumococcal polysaccharide vaccine, as well as serum IgA and IgG measured below the normal ranges. The patient was prescribed a successful, weekly regimen of 15 g of oral intravenous immunoglobulin (IVIG) ten percent liquid (Gammaplex\(^\circledR\) 10%, 5 gm/50 mL).

Conclusion: Oral human IVIG is a novel treatment and has been infrequently utilized for management of chronic rotavirus, necrotizing enterocolitis, diarrhea, HIV enteropathy, irritable bowel syndrome, and malnutrition. This is the first case of recurrent ascending cholangitis as the primary manifestation of CVID, as well as successful treatment of this condition with oral IVIG, in the literature.

Introduction:
Common variable immunodeficiency (CVID) is a heterogeneous group of primary immune deficiency disorders (PIDD) characterized by heightened susceptibility to hypogammaglobulinemia, insufficient vaccination responses, autoimmune and non-infectious inflammatory co-morbidities, and sinopulmonary and gastrointestinal (GI) infections.\(^1\) GI conditions manifest in 20 to 50% of CVID patients and include esophageal candidiasis, diarrhea, nodular lymphoid hyperplasia, autoimmune enteropathy, irritable bowel disease-like colitis, pernicious anemia, gastric adenocarcinoma, B cell immunophenotype lymphoma, and cholangitis.\(^2,5\) Three studies have reported associations of cholangitis and CVID or primary immunodeficiencies,\(^3,5\) although we report the first case of recurrent ascending cholangitis as the primary manifestation of CVID. In addition, this case demonstrated the first reported successful treatment of this condition with oral human intravenous immunoglobulin (IVIG).

A 61-year-old female with a history of cholecystectomy and gastric bypass presented with recurrent ascending cholangitis every other week for eight years. After a hepaticojunostomy to correct a bile duct stricture complication from the cholecystectomy, the patient had been experiencing...
recurrent episodes of right upper quadrant (RUQ) pain with fever. Over a 10-month period, the patient had been prescribed seven courses of oral antibiotics, including ciprofloxacin and metronidazole. These were increased to three per course, followed by biweekly regimens. Ascending cholangitis was diagnosed by fever and RUQ pain in the clinical presentation and supported by CT and MRI imaging revealing pneumobilia.

Both serum IgA and IgG measured below the normal ranges, at 58 mg/dL (normal range, 70-400 mg/dL) and 571 mg/dL (normal range, 700-1600 mg/dL), respectively. The pneumococcal vaccination did not elicit a serologic response. Alkaline phosphatase (ALP, 216 U/L) and alanine aminotransferase (ALT, 82 U/L) levels were above the normal limits.

The patient began a weekly regimen of 15 g of oral IVIG ten percent liquid (Gammaplex® 10%, 5 gm/50 mL). After the first two courses of oral IVIG, the patient did not experience symptoms of cholangitis. She continued this treatment plan without return of symptoms.

Discussion:

International interest in utilizing oral human, bovine, or chicken egg–derived Ig for prophylaxis and treatment of childhood malnutrition and gastrointestinal conditions, emerged several decades ago. Several studies preventing necrotizing enterocolitis or managing rotavirus diarrhea offer evidence of reduced symptoms through this novel route of administration. Losonsky et al. reported approximately 25% recovery of chronic diarrhea or rotavirus, as well as recovered immunological activity in three children with unspecified immune deficiency.

Due to its antigen-neutralizing activity and anti-inflammatory property, orally administered Ig may lower risk of systemic allergic response, hematological diseases, and endotoxin absorption. Oral Ig may improve intestinal barrier function and, thus, prevent increased permeability, which may manifest in severely ill patients with higher susceptibility to endotoxemia and sepsis. Most studies assessing effectiveness of orally-administered Ig (particularly IgG) from human or bovine serum indicate resistance of degradation from gastric acid and proteolytic enzyme exposure. The physical properties of Ig fragment enable sustained active binding and reduced bacterial enterotoxin, endotoxin, and exotoxin activity. However, further controlled studies are necessary to investigate the optimal dose and mechanisms of this novel route of IVIG administration.

PIDD GI or hepatobiliary complications may manifest as infections, autoimmune phenomena, unregulated inflammatory conditions, malignancies, and diseases secondary to therapeutic intervention. GI conditions are reported in up to 50% of CVID patients, with infectious diarrhea as the most common symptom. Gastric adenocarcinoma, immune-mediated enteropathy, nodular lymphoid hyperplasia of the GI tract, small intestine bacterial overgrowth, small bowel villous atrophy, and gastritis have also been noted in CVID cases. Hepatic manifestations, most commonly hepatitis and liver granulomas, are less frequent but have been documented in 9 to 12% of patients with CVID. Autoimmune liver diseases, such as primary biliary cirrhosis and autoimmune hepatitis, and nodular regenerative hyperplasia (NRH) are rare but have also been noted in the literature.

There are sparse publications reporting hepatobiliary manifestations of CVID, such as cholangitis. Mahdavinia et al. described the first two CVID cases associated with primary sclerosing cholangitis (PSC), an inflammatory autoimmune liver disease of chronic biliary epithelium causing chronic cholestasis, multifocal bile duct strictures, and potential complications of cirrhosis and malignancy. A 66-year-old male presenting with pruritus and elevated liver enzyme was diagnosed with PSC, supported by endoscopic retrograde cholangiopancreatography and liver biopsy. After a decade of recurrent urinary tract infections, Clostridium difficile, ulcerative colitis, pneumonias, low immunoglobulin titers and negative PPSV23 confirmed a CVID diagnosis. Mahdavinia et al. also detailed a 29-year-old female CVID patient with a history of recurrent sinopulmonary, urinary tract, and giardia infections, presenting with pruritus, fatigue, and elevated liver enzymes. Magnetic resonance cholangiopancreatogram and liver biopsy verified a PSC diagnosis. Both CVID cases were managed with IVIG. Germinaro et al. documented a CVID case diagnosed after presentation of hypogammaglobulinemia and numerous episodes of
pneumonia, sinusitis, and cholangitis. IVIG and later subcutaneous IgG treatment significantly reduced the frequency of infections. A study by Pikkarainen et al. investigated the gastrointestinal phenotype of CVID in a cohort of 105 Finish patients, five of which were diagnosed with PSC or CVID-associated cholangitis. The present report of recurrent ascending cholangitis is the first specifically noted in the literature but none of the previously described cases associating CVID and cholangitis pursued oral administration of IVIG. Successful treatment of CVID-associated manifestations with oral IVIG has been reported in the literature. Rosario et al. illustrated two reports of successful oral IVIG treatment for CVID-associated GI manifestations, specifically chronic refractory diarrhea.

Conclusion:

PIDDs, such as CVID, classically presents with a variety of infections and other clinical manifestations, some of which involve the GI and hepatobiliary systems. Few studies associate CVID and cholangitis. The present case report is the first to describe recurrent ascending cholangitis in a CVID patient. We propose oral IVIG therapy, which has only been described for diarrhea and necrotizing enterocolitis treatment or prophylaxis in recent literature. Early diagnosis of CVID and accompanied GI and hepatic complications enable appropriate treatment and improve quality of life. More clinical studies are integral to determine the appropriate preventative and treatment measures for CVID-associated GI and hepatic morbidities.

Author Contributions:

All authors contributed to the conception or design of the work, or the acquisition, analysis, or interpretation of the case report. MR and JP participated in the drafting of the manuscript. TA, JS, and RH critically revised the manuscript. All authors approval the final version of the manuscript to be published.

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