PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Diagnosis and Treatment of Gastrointestinal Disorders in Patients With Primary Immunodeficiency

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Gastrointestinal disorders such as chronic or acute diarrhea, malabsorption, abdominal pain, and inflammatory bowel diseases can indicate immune deficiency. The gastrointestinal tract is the largest lymphoid organ in the body, so it is not surprising that intestinal diseases are common among immunodeficient patients. Gastroenterologists therefore must be able to diagnose and treat patients with primary immunodeficiency. Immune-related gastrointestinal diseases can be classified as those that develop primarily via autoimmunity, infection, an inflammatory response, or malignancy. Immunodeficient and immunocompetent patients with gastrointestinal diseases present with similar symptoms. However, intestinal biopsy specimens from immunodeficient patients often have distinct histologic features, and these patients often fail to respond to conventional therapies. Therefore, early recognition of symptoms and referral to an immunologist for a basic immune evaluation is required to select appropriate treatments. Therapies for primary immunodeficiency comprise immunoglobulin replacement, antibiotics, and, in severe cases, bone marrow transplantation. Treatment of immunodeficient patients with concomitant gastrointestinal disease can be challenging, and therapy with immunomodulators often is required for severe disease. This review aims to guide gastroenterologists in the diagnosis and treatment of patients with primary immunodeficiency.

Keywords: Immune System; Hypogammaglobulinemia; IBD; Inflammatory Intestinal Disease.

Primary immunodeficiencies are a group of more than 150 disorders, often inherited, that are caused by intrinsic defects in the immune system. The immune defects can affect the humoral (B cell) immune system, such as in Bruton's agammaglobulinemia; the cellular (T cell) immune system, such as in DiGeorge syndrome; and both T- and B-cell immunity, such as in severe combined immunodeficiency (SCID)[1,2] and in innate defects.

Gastrointestinal (GI) disorders present in 5% to 50% of patients with primary immunodeficiencies. This is in part because the gut is the largest lymphoid organ in the body, containing the majority of lymphocytes and producing large amounts of immunoglobulin (Ig). The mucosal immune system is uniquely regulated to manage its constant exposure to viruses, parasites, and bacterial antigens, all of which are in close proximity to a large reservoir of lymphocytes, macrophages, and dendritic cells. Its response is one of suppression or tolerance, unlike the systemic immune system. Dysfunction of the regulatory mechanisms maintaining this balance between active immunity and tolerance in the gut may lead to mucosal inflammation and damage and GI diseases. Therefore, it is not surprising that GI disorders are common manifestations, and often the initial presenting symptom, in patients with dysfunction in humoral immunity or cell-mediated immunity (Table 1).

GI manifestations can be broadly classified into 4 groups: infection, inflammation, malignancy, and autoimmune. The diversity of disorders involving the GI tract speaks to the differing forms of immune regulation along the length of the intestine, and the varying nature of the challenge (ie, food antigens in the small bowel and commensal flora in the colon). Many of these disorders mimic classic forms of disease (in the absence of immunodeficiency) such as celiac sprue, inflammatory bowel disease (IBD), and pernicious anemia but differ in pathogenesis and are often unresponsive to conventional therapies.

This review highlights the GI manifestations of the more common primary immunodeficiency disorders, focusing on the recognition of these diseases, appropriate diagnostic testing, and therapy.

Predominantly Antibody Deficiency

Selective Immunoglobulin A Deficiency

The most common primary immunodeficiency, estimated at 1 in 300 to 700 in Caucasians, is selective IgA deficiency (IgA $<$ 7 mg/dL with normal or increased levels of other

Abbreviations used in this paper: 6-MP, mercaptopurine; AZA, azathioprine; CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; FOXP3, forkhead box P3; GI, gastrointestinal; GVHD, graft-versus-host disease; IBD, inflammatory bowel disese; Ig, immunoglobulin; IL, interleukin; IPEX, immune dysfunction, polyendocrinopathy, enteropathy, X-linked; NLH, nodular lymphoid hyperplasia; SCID, severe combined immunodeficiency; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; WAS, Wiskott–Aldrich syndrome; WASp, Wiskott–Aldrich syndrome protein; XLA, X-linked agammaglobulinemia.

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immunoglobulins).[3,4] IgA deficiency is not well defined from a genetic aspect; the decreased IgA production may be the result of immune dysfunction in the regulation of terminal maturation of B cells into IgA-secreting plasma cells.[5–7] The majority of patients are asymptomatic, although the absence of IgA has been associated with recurrent upper respiratory infections (frequently in those with concomitant IgG2 subclass deficiency), autoimmune disorders, and allergic diseases.[4,8] T-cell immunity as well as natural killer activity appears to be normal in most patients. In addition, certain HLA haplotypes, including B8 and DR3, are associated with selective IgA deficiency.[9–11]

Although secretory IgA is the major antibody in the intestinal mucosa, the prevalence of GI disorders in patients with IgA deficiency is not as high as one would expect. It is thought that the transportation of IgM from the mucosa into the intestinal lumen by the polymeric immunoglobulin receptor can compensate for the lack of IgA in the intestine and mucosal surfaces, although several studies have challenged this belief.[12–16] There is, however, a demonstrated link between IgA deficiency and giardiasis, celiac disease, nodular lymphoid hyperplasia (NLH), ulcerative colitis, Crohn's disease, pernicious anemia, and gastric and colonic adenocarcinoma[17]; these disorders, however, are associated much more commonly with common variable immunodeficiency (CVID).

GI infections related to *Giardia lamblia* have been reported with an increased frequency in primary immunodeficiency patients.[18] Once ingested, *G lamblia* cysts release trophozoites, which colonize the small intestine and cause bloating, cramping, excessive flatus, and watery diarrhea. Steatorrhea and villus flattening can occur with chronic infection owing to effacement of the mucosa and the subsequent disruption of the absorption of lipids and carbohydrates. The degree of mucosal damage appears to be associated with the duration of the infection; some epithelial damage may be irreversible. Diagnosis is made by examining the stool for cysts or trophozoites of *G lamblia*, or by examination of duodenal aspirates, which can yield more determinate results. The parasitic load can be unremitting in IgA-deficient patients, despite treatment with metronidazole. Luminal IgA may be involved in clearing this parasite, as shown in studies on jejunal biopsy specimens from infected patients who stained positive for anti-human IgA. Presumably the lack of secretory IgA in these patients allows for attachment and proliferation of the organism on the intestinal epithelium; however, mouse models have suggested that clearance is T-cell mediated.[19]

The association between celiac disease and IgA deficiency frequently is reported as having a causal relationship, although the association of these 2 diseases may have a genetic basis, given shared HLA haplotypes. Genetic studies have shown that an important susceptibility locus between celiac disease and IgA deficiency is haplotype HLA-A1, Cw7, B8, DR3, and DQ2,[20–23] and celiac disease is associated with HLA-DQ2 and DQ8.[20,21,23] However, given the high incidence of both disorders, between 1 in 100 and 1 in 300 in the population, it is conceivable that the presence of one disease in the setting of the other is purely coincidental.

Secretory IgA can bind to wheat gluten and gliadin, and the absence of IgA may lead to abnormal processing of these antigens. Symptoms of celiac disease are similar in patients with or without IgA deficiency. The histopathology of celiac disease in IgA-deficient patients is indistinguishable from the pathology seen in patients with conventional celiac disease: increased numbers of intraepithelial lymphocytes, villous shortening or flattening, crypt hyperplasia, and infiltration of the lamina propria with lymphoid cells. A distinguishing feature is the absence of IgA-secreting plasma cells in intestinal biopsy specimens in IgA-deficient patients.[24–26] Antigliadin IgA, antitissue transglutaminase IgA, and antiendomysial IgA antibodies cannot be used as screening tests for this population, which is why some celiac panels come with a measurement of serum IgA to rule out the possibility of IgA deficiency.[26] Tissue transglutaminase IgG may be a better screening test.[27–29] Celiac disease associated with IgA deficiency is responsive to gluten withdrawal, unlike the flat villous lesion seen in CVID.[30–32] Failure to respond to a gluten-free diet should lead one to consider CVID.

NLH also is reported in IgA deficiency. These nodules often appear in multiples and are commonly 5 mm or greater in diameter. They are found in the lamina propria, superficial submucosa of the small intestine, or both, and occasionally can occur in the stomach, large intestine, or rectum. The lesions can be associated with mucosal flattening, causing malabsorption and even obstruction when large. Diagnosis is made by small-bowel enteroscopy or contrast barium studies.[33] Immunohistochemical staining demonstrates that these nodules contain large amounts of IgM-bearing cells, possibly as compensation for the absent IgA.[34] These nodules are very sensitive to oral steroids.[35] When presented with IgA deficiency, NLH also has been associated with lymphomas (usually B-cell origin)[36] and gastric carcinomas.[37]

Other GI manifestations reported in patients with IgA deficiency include pernicious anemia,[38–40] Crohn's disease, and ulcerative colitis.[41–44]

Asymptomatic patients with IgA deficiency are generally not treated. Patients with GI manifestations should be treated in the same way as patients without this immunodeficiency. Current preparations of Ig do not contain sufficient amounts of IgA; therefore, patients with IgA deficiency should receive treatment for specific complications and should be monitored over time because some may progress to CVID. Because patients with IgA deficiency may have IgG or IgE antibodies to IgA (although rare), serious reactions may occur if these patients receive blood products. In cases in which blood transfusion is required, the patient should be screened for anti-IgA antibodies, and blood product should be prepared from an IgA-deficient individual or saline-washed.

X-Linked Agammaglobulinemia

X-linked agammaglobulinemia (XLA) results from a defect in Bruton's tyrosine kinase, an intracellular kinase, leading to the maturation arrest of pre-B cells and subsequent failure of the generation of mature B cells.[45] The incidence is approximately 1 in 100,000 live births. The diagnosis of XLA typically is made in a male infant with recurrent sinopulmonary infections beginning at 4 months of age, when maternal antibodies are depleted. Laboratory findings include a profound reduction in all classes of immunoglobulin caused by the failure of B cells to differentiate into plasma cells, and humoral responses to specific antigens are markedly depressed or absent. Peripheral $CD19^+$ B cells are usually less than 0.1%.[46] T-cell numbers and function are normal.