Gastrointestinal Manifestations in Primary Immune Disorders

Shradha Agarwal, MD and Lloyd Mayer, MD

Abstract: The gastrointestinal tract is the largest lymphoid organ in the body containing T and B lymphocytes, macrophages, and dendritic cells. Despite the fact that these cells are constantly confronted with antigen primarily in the form of food and bacteria, immune responses in the gut are tightly regulated to maintain homeostasis. Without this balance of active immunity and tolerance, mucosal inflammation may ensue, and manifest as Crohn's disease, ulcerative colitis, pernicious anemia, or celiac sprue. Therefore, it is not unreasonable that inflammatory diseases of the gut are commonly encountered in patients with primary immune deficiencies. The exact pathogenesis of gastrointestinal diseases in the setting of primary immunodeficiency remains unknown, however, both humoral and cell-mediated immunity appear to play a role in preventing intestinal inflammation. Patients presenting with atypical gastrointestinal disease and/or failure to respond to conventional therapy should be evaluated for an underlying primary immune disorder in order to initiate appropriate treatment, such as immunoglobulin or in more severe cases bone marrow transplantation, to prevent long term complications.

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Key Words: primary immune disorders, immunodeficiency, gastrointestinal disease, inflammatory bowel disease

Primary immune deficiencies include a group of over 100 disorders caused by intrinsic defects in the immune system and are often inherited genetic disorders. 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, both T and B cell immunity, such as in severe combined immunodeficiency (SCID), or neutrophil and macrophage defects, such as in chronic granulomatous disease (CGD). Defects in innate and acquired immunity lead to impaired immune responses and patients may subsequently develop recurrent infections such as pneumonia or bronchitis. Depending on the type of immune defect, patients may develop a host of other clinically relevant conditions such as autoimmune disease, bronchiectasis, and malignancy in association with their underlying immunodeficiency. Since the gastrointestinal (GI) tract is the largest lymphoid organ in the body, it is not surprising, that GI conditions are common, and often the initial presenting problem, in patients with underlying immunodeficiency disorders.

The mucosal immune system is uniquely regulated. Its response is one of tolerance or suppression, unlike the systemic immune system, because of its constant exposure to food and bacterial antigens adjacent to a large reservoir of lymphocytes, macrophages, and dendritic cells (DCs). Dysfunction of the regulatory mechanisms maintaining the balance between active immunity and tolerance in the gut may lead to mucosal damage and GI diseases such as inflammatory bowel disease (IBD), celiac sprue, or food allergy. Although the exact pathogenesis of these diseases remains unknown, both humoral and cell-mediated immunity appear to be important in preventing damage to the intestinal tract.

GI manifestations associated with primary immunodeficiencies can be divided into 4 categories: infection, malignancy, inflammatory, and autoimmune. Many of these disorders mimic classic forms of the disease (in the absence of immunodeficiency) such as celiac sprue, IBD, and pernicious anemia, but differ in pathogenesis and are often unresponsive to conventional therapies. Treatment for immune deficiency syndromes includes administration of immunoglobulin (Ig) (intravenous or subcutaneous) and antibiotic therapy to reduce the frequency and severity of infections. In more severe deficiencies, bone marrow transplantation may be required. However, GI diseases are not treated by Ig since preparations contain IgG, which cannot reach the lumen of the intact gut, and very little IgA or IgM. Therefore, at this time treatment for GI disease associated with immunodeficiency syndromes is guided by successful therapy used for similar disorders in immunocompetent patients with additional caution when immunosuppressive agents are administered.

This review focuses on the GI manifestations of primary immunodeficiency disorders followed by an overview of the basic evaluation for immune competence as summarized in Table 1. We have additionally included

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From the Division of Clinical Immunology, Mount Sinai School of Medicine, New York, New York.

Reprints: Shradha Agarwal, MD, Mount Sinai School of Medicine, Division of Clinical Immunology, One Gustave L. Levy Place, Box 1089, New York, NY 10029 (e-mail: shradha.agarwal@mssm.edu)

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TABLE 1. Evaluation of Immune Disorders with Associated Gastrointestinal Manifestation

Immunodeficiency	Evaluation with Clinically Significant Result	Gastrointestinal Manifestation
Common variable immunodeficiency (CVID)	Quantitative immunoglobulins→reduced serum IgG and IgA and/or IgM Antibody response (IgG) to vaccination→poor, nonprotective Lymphocyte subsets→normal or reduced B cell numbers	Diarrhea, nodular lymphoid hyperplasia, flat villous lesions, IBD-like disease, pernicious anemia[34,39,47,48,54,58,67]
Selective IgA deficiency	Quantitative immunoglobulins→serum IgA absent or near absent usually <10 mg/dl; normal IgG and IgM levels though IgG2 subclass deficiency may be present	Diarrhea, celiac sprue, nodular lymphoid hyperplasia[8,9,11,16,21–23,25–27,29,89–92]
Agammaglobulinemia, X-linked or autosomal recessive (AR)	Quantitative immunoglobulins→reduced serum levels of all immunoglobulins Antibody response (IgG) to vaccination→poor, nonprotective Lymphocyte subsets→normal numbers of pro-B cells; reduced/absent B cells	GI disorders rare, chronic diarrhea, malabsorption[32,33,37,40,41,93]
X-linked hyper IgM syndrome	Quantitative immunoglobulins→normal to elevated IgM levels; low IgG and IgA Antibody response (IgG) to vaccination→poor, nonprotective Lymphocyte subsets→normal T cell numbers; B cell numbers are normal or slightly reduced	Diarrhea, progressive liver disease, sclerosing cholangitis[94–97]
Severe combined immunodeficiency	Lymphocyte subsets→markedly diminished T cells; variable B cell and NK cell numbers depending on functional deficiency *In vitro* assay of lymphocyte function→diminished response to mitogens-PHA, ConA, PWM	Diarrhea, oral candidiasis[1,98]
DiGeorge syndrome	Quantitative immunoglobulins→immunoglobulins are usually normal though occasionally IgE is elevated and IgA may be reduced Lymphocyte subsets→variable decreases in T lymphocytes; B and NK cells are normal or elevated *In vitro* assay of lymphocyte function→variable lymphocyte response to mitogens depending on thymic deficiency	Mucocutaneous candidiasis[98–100]
Immune dysregulation, polyendocrinopathy, enteropathy (IPEX) syndrome	Complete blood count→eosinophilia Quantitative immunoglobulins→may have increased serum IgE and IgA Lymphocyte subsets→CD4+CD25+ T cells are reduced most patients with FOXP3 mutations have markedly decreased or absent FOXP3+ Tregs; otherwise normal T-cell and B-cell subsets *In vitro* assay of lymphocyte function→specific antigens are normal or slightly decreased	Severe enteropathy with watery often bloody diarrhea associated with eosinophilic inflammation[101-104]
Bare lymphocyte syndrome	Quantitative immunoglobulins→variable reductions Antibody response (IgG) to vaccination→poor, nonprotective Lymphocyte subsets→low numbers of CD4+ T cells with proportional increases in CD8+ T cells Flow cytometry-diminished expression of MHC *In vitro* assay of lymphocyte function→impaired antigen specific responses	Progressive liver disease, sclerosing cholangitis[105]

(*Continued*)

TABLE 1. (*Continued*)

Immunodeficiency	Evaluation with Clinically Significant Result	Gastrointestinal Manifestation
Chronic granulomatous disease (CGD)	Dihydrorhodamine reductase (DHR) or nitroblue tetrazolium (NBT)→diminished respiratory burst in neutrophils	Colitis, hepatic abscess, gastric outlet obstruction, small bowel obstruction, granulomatous stomatitis, oral ulcers, esophageal dysmotility[73,76,77]
Wiskott-Aldrich syndrome	Complete blood count→platelet numbers are reduced and small in size	Colitis, bloody diarrhea, malabsorption[106–108]
	Quantitative immunoglobulins→variable concentrations secondary to accelerated synthesis and catabolism of Igs (usually low IgM, elevated IgA and IgE, and normal or slightly low IgG)	
	Antibody response (IgG) to vaccination→impaired antibody response	
	Lymphocyte subsets→moderate reductions in percentages of CD3, CD4, and CD8 bearing T cells	
	In vitro assay of lymphocyte function→impaired lymphocyte response to mitogens	
Hermansky-Pudlak Syndrome	Complete blood count→normal platelet count	Granulomatous colitis[82–84]
	Coagulation studies→prolonged bleeding time, with abnormal platelet function assays	

several other immune disorders with GI disease that may be reviewed in the literature as a reference.

SELECTIVE IgA DEFICIENCY

Selective IgA deficiency is the most common primary immunodeficiency, with a prevalence of ≈1 in 300 to 700 individuals.[1] The mechanism underlying the development of IgA deficiency is defective terminal maturation of B cells into IgA-secreting plasma cells, causing reduced amounts of serum IgA (usually <7 mg/dL) but normal serum IgG and IgM levels.[2] The majority of IgA-deficient patients are asymptomatic and require no treatment. Cases associated with infection, such as sinusitis or pneumonia, may have a concomitant IgG subclass deficiency and represent a form of common variable immunodeficiency (CVID).[3,4] Although IgA is the most abundant antibody in the gut, the prevalence of GI disorders in this deficiency is not high. It is thought that IgM, which can be transported by secretory component from the mucosa into the intestinal lumen, may compensate for the lack of IgA.[5–7]

Of the GI disorders that are present in IgA deficiency the most frequent are celiac disease, giardiasis, and nodular lymphoid hyperplasia (NLH)[8]; however, these diseases occur more commonly in CVID. There is a 10-fold increased risk for celiac disease in patients with IgA deficiency. Genetic studies demonstrate that an important susceptibility locus is associated with the ancestral haplotype, HLA-A1,Cw7,B8,DR3,DQ2, and celiac disease is associated with HLA-DQ2 and DQ8.[9–12] However, given the relatively high incidence of IgA deficiency and celiac disease independently, it is possible that the incidence of their occurrence together is coincidental.

Symptoms of celiac disease at presentation are similar in patients with or without IgA deficiency, but 1 study observed a higher prevalence of silent forms of disease in those with concommitant IgA deficiency,[13] suggesting that these patients should be screened for celiac disease upon initial diagnosis. Serologic diagnosis of celiac disease requires the presence of antibodies, both IgG and IgA, against tissue transglutaminase (anti-tTG), which is highly sensitive, specific, and more cost-effective than other antibody tests. However, in IgA deficiency the IgA-specific antibodies are not seen and in such cases a total IgA should be measured if the diagnosis of IgA deficiency has not already been established.[9,13–16] However, serum IgG anti-tTG levels are elevated in IgA deficient patients with coexisting celiac disease and can be used as a diagnostic marker.[17] On histopathology the villous atrophy seen in celiac disease associated with IgA deficiency is identical to that seen in patients without immunodeficiency but IgA-secreting plasma cells are absent.[9,13,15,16] Despite these differences in the diagnostic criteria, IgA-deficient patients with celiac disease respond clinically to a gluten-free diet similar to those who are not immunocompromised.[18,19]

An infectious cause of chronic diarrhea in IgA deficiency as in other primary immunodeficiencies is *Giardia lamblia*. Chronic infection can result in steatorrhea and villous flattening secondary to trophozoites effacing the mucosa and disrupting the absorptive capacity for lipids and carbohydrates. The extent of mucosal damage appears to

be related to the duration of infection and some epithelial damage may be irreversible. Luminal IgA may play a role in the clearance of this parasite, as studies have shown trophozoites on jejunal biopsy specimens from infected patients that stain positively with fluorescein-conjugated anti-human IgA. Therefore, the lack of secretory IgA in IgA-deficient patients may allow for attachment and proliferation of the organism on the intestinal epithelium. However, mouse models have suggested that the actual clearance of this organism is T-cell-mediated.[20] The diagnosis is made by examination of the stool for cysts or trophozoites of *G. lamblia*, although this is not a very sensitive assay and duodenal aspirates may yield more positive results. Giardiasis can be treated with metronidazole but is often unremitting in IgA-deficient patients.

NLH is also reported in IgA deficiency but is very rare.[21,22] These nodules can occur individually but are usually multiple in number and commonly 5 mm in size and are found largely in the lamina propria and/or superficial submucosa of the small intestine but occasionally in the large intestine, rectum, or stomach. The diagnosis is made by small bowel enteroscopy or contrast barium studies. Immunohistochemical analyses have demonstrated that these nodules contain large numbers of IgM-bearing cells, suggesting (although not proven) that this represents an attempt by the intestine to substitute for the absence of IgA.[23] The lesions may be associated with mucosal flattening leading to malabsorption and, if large enough, the nodules may cause obstruction or be the leading edge of intussuception. Whether or not NLH leads to GI malignancy is controversial, although lymphomas (usually of B cell origin)[24] and gastric carcinomas[25] have been reported in the setting of IgA deficiency. When associated with Giardiasis the diarrhea and malabsorption may be difficult to treat, although the nodules are exquisitely sensitive to oral steroids.

The following GI manifestations have also been reported in isolated case reports in association with IgA deficiency: pernicious anemia[26,27]; Crohn's disease (CD) and ulcerative colitis (UC)[28–30]; lymphomas[24]; and gastric carcinomas.[25] The actual prevalence of these diseases is not defined and whether these patients were purely IgA-deficient and not a variant of CVID is not known.

X-LINKED AGAMMAGLOBULINEMIA (XLA)

X-linked agammaglobulinemia results from a defect in Bruton's tyrosine kinase, an intracellular kinase, which leads to the maturation arrest of pre-B cells and subsequent failure of the generation of mature B cells.[31] All classes of immunoglobulins are absent in XLA due to the failure of B cells to differentiate into plasma cells and CD19+ B cells are usually below 2%.[1] The incidence is ≈1 in 100,000 live births and typically presents in a male infants with recurrent sinopulmonary infections starting at 4 months of age when maternal antibodies are depleted.

Patients with XLA rarely present with GI symptoms, although chronic diarrhea and malabsorption have been reported.[32–34] Intestinal biopsies demonstrate normal morphology and absent plasma cells in the lamina propria similar to what is seen in CVID. Infectious diarrhea, most commonly related to Giardiasis, is likely secondary to bacterial overgrowth and lack of antibody.[35] Enteroviral infections are also clinically important to consider, as case reports of XLA patients with enterovirus have been reported and can lead to severe neurological defects.[36–38] Rare cases of gastric adenocarcinoma and CD-like disease occurring in the small bowel in XLA patients have also been described.[39–41]

COMMON VARIABLE IMMUNODEFICIENCY (CVID)

CVID is the second most common form of immunodeficiency after IgA deficiency. The diagnosis of CVID is established based on reduced levels of 2 serum immunoglobulins, IgG and IgA and/or IgM, at least 2 standard deviations below the age-specific mean values, in addition to impaired specific antibody production in response to vaccination in vivo or recent infections.[1] The hypogammaglobulinemia results from the failure of B cells to differentiate into plasma cells; however, T cell abnormalities and defective cytokine production have also been described.[42–46] As with other B-cell-related immunodeficiencies CVID patients present with recurrent sinopulmonary infections such as bronchitis, pneumonia, and sinusitis.

There is a strong association with GI disorders and CVID ranging from 20%–60% of patients in various studies.[34,39,47–49] Hermans et al[49] reported that 60% of patients with CVID had chronic diarrhea with steatorrhea and/or giardiasis, achlorhydria, abnormal Schilling test, or morphological abnormalities on small intestinal biopsy. In addition, 42% had malabsorption and 8% had splenomegaly. Similarly, Hermaszeski and Webster[34] reported 40% of their CVID patients having diarrhea with or without malabsoprtion. In a more recent study cohort of Italian patients with CVID, chronic diarrhea was present in 23% of patients at the time of diagnosis and 56.6% in a study reported from Iran.[35,50] Unlike XLA and IgA deficiency, GI disease is more common in CVID, suggesting that T cell dysfunction contributes to the pathogenesis of intestinal disease. No significant correlation between GI disorders and levels of IgG, IgA, or IgM has been demonstrated, although data from our institution have shown that patients with abnormal T-cell function were more likely to have GI disorders.[51]

In the past, cases of diarrhea were thought to be secondary to *Giardia* and patients were treated empirically. Chronic Giardiasis can lead to villous flattening, as seen in

celiac disease.[52] It often has a prolonged course despite treatment with metronidazole reflecting the diminished ability of patients to eradicate the organism.[53] Stool should be examined specifically for cysts or trophozoites of *Giardia*, although the diagnosis is not easily made, making it necessary to examine the duodenal fluid or intestinal biopsy. Excessive loss of protein into the GI tract may cause abnormalities in serum chemistries. Other unusual infections reported include *Cytomegalovirus* and *Cryptosporidium*.[54] One would expect a high incidence of *Clostridium difficile*, given the frequent use of antibiotic therapy in these patients; however, this is not seen, possibly related to the presence of high titers of anti-*C. difficile* antibody in IVIg, which may leak into the GI tract.[55,56]

Inflammation of the small and large intestine is reported to be present in 2%–13% of patients with primary immunodeficiency and includes autoimmune inflammation phenomena such as pernicious anemia, malabsorption from flat villous lesions and IBD.[57,58] The diagnosis of pernicious anemia in CVID patients is often made 20 years earlier than in someone who is immunocompetent and has the disease.[59] In classical pernicious anemia autoantibodies contribute to disease pathogenesis; however, in CVID-associated pernicious anemia, no antiparietal cell antibodies are detected, suggesting that this process is T-cell-mediated. There is gastric atrophy and lymphocytic infiltration in the mucosa but an absence of plasma cells in CVID-affected patients.[59] Treatment is similar to those with classic pernicious anemia, with replacement of B_{12} monthly and monitoring for malignant changes in the gastric mucosa, as associated achlorhydria may predispose patients to gastric carcinomas.[60]

Another common GI manifestation of CVID is the flat villous lesions in the small intestine with associated diarrhea, weight loss, and fat malabsorption resembling what is seen in classical celiac sprue.[61] On histologic examination there are short villi, crypt hyperplasia, and intraepithelial lymphocytosis in both classic celiac disease and flat villous lesions in CVID. However, in CVID, plasma cells are absent in intestinal biopsies, while in classic celiac disease plasma cells are increased in number with a concomitant increase in secreted IgA and IgM antibody. There has been evidence of J-chain synthesizing B cells in the gut of CVID patients; however, the absence of plasma cells in the intestinal biopsy suggests that these cells fail to differentiate.[62] In addition, there is a lack of antibodies to gliadin, reticulin, tissue transglutaminase, and endomysium as well as the absence of celiac-associated genes (HLA DQ2/DQ8) in CVID patients. These findings suggest that the villous flattening in CVID is mediated by T cells. Unfortunately, patients continue to have malabsorption and weight loss since gluten withdrawal is ineffective in patients with CVID and sprue-like disease, further suggesting that this condition is mechanistically distinct from classic celiac disease. Patients should have adequate replacement with water-soluble vitamins and antiresorptives for the prevention of osteoporosis. For severe cases of malabsorption an elemental diet or total parental nutrition may be required, keeping in mind that an indwelling catheter is a source for infection.[63] Low-dose corticosteroids can be used; however, higher doses can lead to a significant risk of opportunistic infections and a trial of immunomodulator therapy (AZA/6MP) should be undertaken.

Hermaszweski and Webster[34] reported a prevalence of IBD in CVID patients of 4%. Both CD- and UC-like disease have been observed; however, whether this is true IBD remains to be determined. It appears that patients with CVID are predisposed to develop an IBD-like disease while those with XLA are not, suggesting that this tendency toward inflammation is driven by T cells or more likely T-cell dysregulation. Cytokine knockout mice develop GI diseases resembling UC and CD,[64–66] demonstrating that immune dysregulation is poorly tolerated in the gut and that mucosal inflammation may be the default pathway in the setting of such a dysregulated state. In CVID patients with IBD-like disease, colonic biopsies demonstrate an absence of plasma cells in the lamina propria, intraepithelial or subepithelial lymphocytosis (microscopic or lymphocytic colitis), prominent apoptosis, granulomas, and crypt distortion.[54] A recent study by Mannon et al[67] demonstrated that lamina propria mononuclear cells from symptomatic CVID patients produced significantly higher IFN-γ driven by high levels of IL-12 in the absence of IL-23 or IL-17, unlike control patients with CD, suggesting an alternate pathway of inflammation in CVID. Mechanic et al[68] reported a group of CVID patients with diffuse granulomatous disease, including the colon, who displayed severe T-cell dysfunction. In another study, persistent activation of the tumor necrosis factor pathway was reported in a subgroup of CVID patients, with decreased numbers of CD4+ lymphocytes in peripheral blood, splenomegaly, and persistent immune activation of monocytes/macrophages, suggesting that this activation may contribute to clinical manifestations in CVID patients.[69] Treatment of IBD occurring in association with CVID is generally the same as for nonimmunodeficient patients, although gut inflammation in CVID patients may seem to be more difficult to control. Unfortunately, replacement immunoglobulin has not been shown to prevent or treat the intestinal inflammation. Antibiotics such as metronidazole or ciprofloxacin, antiinflammatory agents such as 5-aminosalicylic acid (5-ASA), topical steroids, or suppositories can be used. Immunomodulators, azathioprine/6-mercaptopurine (AZA/6MP), can be used safely given that the doses used are too low to affect systemic T-cell function. Several groups have demonstrated improvement using infliximab

but care should be taken to monitor for fungal infections in patients with severe T-cell defects.[69,70]

GI malignancy is also more common in CVID patients, in comparison to IgA deficiency or XLA, especially in the fifth and sixth decade of life.[34,71] Hermans et al[49] reported 50% of the patients in their CVID cohort had either GI carcinoma or lymphoma. Those with a history of chronic atrophic gastritis with achlorhydria, intestinal metaplasia, and pernicious anemia have an increased risk of developing gastric cancer.[60] Benign lymphoproliferative disorders such as NLH have also been observed in 8% of patients in a recent study.[50] The cause is still unknown but it has been suggested (although not proven) that the lymphoid hyperplasia is a compensatory response for the antibody deficiency. However, treatment with IVIg has not been shown to correct this. As in IgA deficiency, NLH usually presents as multiple discrete nodules upwards of 5 mm in size commonly located in the upper small intestine and occasionally in the colon or stomach; immunocompetent subjects with NLH usually develop nodules in the distal ileum and proximal colon.[72] The hyperplasia may lead to villous flattening and in more severe cases may cause malabsorption, intussusception, or obstruction. Whether NLH can lead to the development of lymphoma is controversial.

CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease (CGD) is a rare (1 in 200,000 in US births) immunodeficiency syndrome caused by the inability of the phagocytes to produce adequate reactive oxygen metabolites to kill ingested microorganisms. Patients suffer from recurrent infections at epithelial surfaces (skin, gut, lungs) in contact with the environment as well as in organs with large numbers of reticuloendothelial cells such as the liver.[73]

Up to 50% of patients with CGD have GI complications ranging from noncaseating granulomatous colitis, protein losing enteropathy, and inflammatory disease mimicking CD. The rate of gut involvement has been reported to be higher in the X-linked gp91^{phox} deficiency compared to the autosomal recessive forms of the disease.[74] CGD patients may present with granulomatous lesions, either at diagnosis or later, throughout the GI tract from the oral cavity to the colon causing dysphagia, dysmotility, or obstruction. It is speculated that chronic antigenic stimulation from organisms persisting within and not killed by phagocytes results in granuloma formation and bowel wall thickening.[75]

The gut inflammation is chronic and relapsing, with a phenotype overlapping that seen in CD and UC. Endoscopy reveals features similar to idiopathic IBD, with colonic narrowing, a cobblestone pattern, thickened bowel wall, fistulization, pancolitis, patchy friability, pseudopolyps, and hemorrhage.[73,76] Microscopically there are large granulomas usually in the muscularis, submucosal edema, crypt abscesses, and lipid-laden histiocytes. Treatment options, including immunomodulators, are based on established IBD therapies. However, reports of infectious complications may preclude their use in the CGD population. We have reported a case of successful therapy with granulocyte-macrophage colony stimulation factor (GM-CSF) treatment.[77]

Hepatic abscess is also common in CGD and may be recurrent and prolonged. One cohort of 22 CGD patients had 61 cases of hepatic abscesses, with 29 recurrent and 20 persistent.[78] *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the main organisms identified in patients with hepatic abscess; patients present with fever, abdominal pain, fatigue, weight loss, and night sweats.[76] These abscesses require aggressive surgical drainage and antimicrobial therapy based on culture.

HERMANSKY–PUDLAK SYNDROME

Hermansky–Pudlak syndrome (HPS), first described in 1959, is a complex of manifestations including tyrosinase-positive oculocutaneous albinism (Ty-pos OCA), hemorrhagic diathesis secondary to platelet dysfunction, and systemic complications such as renal failure, pulmonary fibrosis, and cardiomyopathy, associated with accumulation of ceroid depositions in the reticuloendothelial system.[79–81] It is a rare autosomal recessive condition with a high prevalence in northwestern Puerto Rico.[82] The associated granulomatous colitis, occurring in ≈15% of patients with HPS, has clinical features suggestive of chronic UC and pathological features similar to that of CD including nonnecrotizing granulomas, fissuring, and transmural inflammation.[82,83] Colitis usually manifests in the first and second decades of disease and can be severe and fatal.[84] It was initially thought that the colitis of HPS is a nonspecific reaction to the tissue deposition of ceroid causing tissue damage and fibrosis, but several other cases of HPS with GI complications related to colitis suggest that it is due to the development of true CD.[85–87] Cases reported in the literature are those that have failed medical treatment such as sulfasalazine, mesalamine, metronidazole, and corticosteroids. A recent review of the literature described 13 patients with HPS requiring surgery for lower GI bleeding, intractable colitis, or perianal disease.[83] There are a few case reports demonstrating good results using repeated infusions of infliximab for treatment suggesting that TNF-α plays a role in this form of colitis; however, treatment should be used with caution as it may increase the risk for infection in primary immunodeficiency.[84,85]

LABORATORY EVALUATION

Clinically, it is important to consider the diagnosis of immunodeficiency in any patient with a history of intractable diarrhea, malabsorption, and failure to thrive who is

resistant to conventional treatments. It is important to distinguish between immunodeficiency secondary to defects in T- and/or B-cells as there appears to be an increased prevalence of GI disease when there are defects in both humoral and cellular immunity.

Measurement of total serum protein, composing albumin, and globulin may provide an initial indication that immunoglobulins may be reduced. Evaluation of a B-lymphocyte defect begins with measurement of antibody production by quantitative immunoglobulins (IgG, IgA, IgM) as well as the qualitative aspect of the antibody response as measured by the ability to make antibodies to antigenic challenge (response to prior vaccinations; MMR, tetanus, diphtheria, Hib, pneumococcus, varicella) in protective amounts.[88] Immunoglobulin levels should be compared to age-specific normal reference ranges. Evaluation of subclass deficiency may be helpful in the assessment of an immunodeficiency especially in the setting of IgA deficiency. In addition, a complete blood count (CBC) and lymphocyte screen to assess the number of lymphocytes and subpopulations (T cells, B cells, CD4+, CD8+ T cells) should be obtained as lymphopenia may occur secondary to excessive loss into the lumen or trapping in the inflamed bowel wall.

Depending on the results of these initial tests, further evaluation may be required for a more detailed investigation of cellular immune function. The lymphocyte proliferation assay is an in vitro assay measuring responses to mitogens and/or antigens. Mitogens are plant-derived lectins that bind to selected carbohydrates on lymphocyte surface glycoproteins and activate intracellular signaling pathways nonspecifically, leading to increased metabolic activity and cell division demonstrated by incorporation of a radioactive marker. Mitogens activate cells without antigenic specificity so that more than 80% of T cells will respond to this form of activation. Phytohemagglutinin (PHA) and concanavalin A (Con A) activate T cells, in contrast to pokeweed (PWM) mitogen that stimulates both T cells and B cells. Normal reference ranges for these proliferation assays are taken from healthy controls and reported as a stimulation index (SI) comparing the stimulated to unstimulated cells. Poor mitogen responses suggest a defect in cell-mediated immunity. Steroid therapy may lead to diminished numbers of T cells and mitogen responsiveness, making interpretation of these tests difficult during therapy.

Detailed testing can be done to investigate specific disorders. For example, suspicion of CGD should lead to further investigation of neutrophil function by nitroblue tetrazolium (NBT) test, chemiluminescence assay, or dihydrorhodamine reductase (DHR) assay to demonstrate a reduction or absence of phagocytic respiratory burst. Contrast imaging should be used to investigate potential obstructive granulomas of the GI tract and hepatic abscesses.

SUMMARY

Given that the GI tract represents the largest lymphoid organ, with a unique mucosal immune system, it is not unreasonable that patients with primary immunodeficiency may present with intestinal diseases. Therefore, any patient who presents with unusual symptoms, atypical GI diseases which may resemble classic forms of IBD or celiac disease, or who fail to respond to conventional therapy should be evaluated for immunodeficiency syndromes. Early evaluation will help initiate critical treatment with Ig replacement, if indicated, improve quality of life, and prevent long-term complications.

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