

Inflammatory Cytokines in a Child with Hypogammaglobulinemia and Nodular Lymphoid Hyperplasia Treated with Oral Budesonide

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We present a 6-year-old boy with recurrent sinopulmonary infections, decreased serum IgG levels, decreased memory and switched B cells, decreased antibody responses to *Streptococcus pneumoniae* immunization, diarrhea, and abdominal pain. Intravenous immunoglobulin was initiated, which resulted in marked improvement of infections. Plasma interleukin (IL)-6 and IL-8 levels were elevated, and subsequent endoscopy and small bowel radiographic studies revealed nodular lymphoid hyperplasia (NLH) affecting the ileum. The NLH was treated with enteric-coated budesonide, which dramatically improved the gastrointestinal symptoms, and the plasma IL-6 and IL-8 became undetectable.

Introduction

NODULAR LYMPHOID HYPERPLASIA (NLH) of the intestine is a relatively uncommon entity seen most often in adults in association with various forms of humoral immunodeficiency.^{1–13} Histologically, it is characterized by the presence of nodules within the lamina propria that consist of lymphoid follicles with enlarged germinal centers; depending upon the severity of the immunodeficiency, plasma cells are varyingly diminished in number.^{7–12} On radiographic examination, there are diffuse and multiple regular filling defects 1 to 3 mm in diameter throughout the segment of involved intestine.^{14–16}

Although NLH is more commonly seen in the small intestine, it can also involve the colon, rectosigmoid, or terminal ileum and colon.^{2,3,14–17} In children, NLH involving only the colon has been considered a benign lesion representing a normal response to a verity of stimuli. Few children with this entity have undergone immunologic studies; however, humoral immunodeficiency has been noted in some with NLH involving either the small intestine or the colon.

Case Report

The patient is a 6-year-old boy with Factor VII deficiency and a history of recurrent otitis media, sinusitis, bronchitis, and pneumonia. HIV-1/HIV-2 antibodies were negative. Immunologic evaluation revealed repeatedly decreased serum IgG levels, 368–456 mg/dL (normal 585–1,565), but

normal levels of IgA and IgM levels (Table 1). Antibody titers to *Hemophilus influenzae* type B (HiB) (<0.11 mcg/mL) and to *Streptococcus pneumoniae* (<2.0 mcg/mL to 12 of 14 serotypes) were initially decreased. Postimmunization titers to HiB were normal but remained decreased to 4/14 serotypes of *S. pneumoniae* 6 weeks postimmunization. Serum albumin levels were normal. CD27+ memory, 14% (normal 25%–40%), and IgD-CD27+ switched B cells, 5% (normal ≥6%), were decreased. The percentage of CD4+ T cells were decreased, 28% (normal 31%–47%), but the number of CD4+ T cells was normal, 741 cells/mm³ (normal 650–1,500 cells/mm³). Lymphoproliferative responses to phytohemagglutinin, concanavalin A, and pokeweed mitogen were normal; however, lymphoproliferative responses to *Candida albicans* and to tetanus toxoid were decreased (Table 1). Prophylactic antibiotics were begun, but subsequently intravenous immunoglobulin (IVIG) was begun. With IVIG therapy, the patient had marked decrease of infections.

Medical history was significant for Factor VII deficiency manifested by increased bleeding with tonsillectomy 2 years previously, easy bruising, and recurrent epistaxis. The patient also had a history of abdominal pain, intermittent diarrhea, and bright red blood with some bowel movements. Colonoscopy performed 1 year previously was normal. Perianal skin cultures were negative for group A *Streptococcus*; stool cultures were negative for *Salmonella*, *Shigella*, *Campylobacter*, and *Escherichia coli* O157. Stool specimens were negative for ova and parasites. Duodenal biopsy was negative for *Giardia lamblia*. Gastric biopsy was negative gastritis and for *Helicobacter pylori*. The symptoms of

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TABLE 1. IMMUNOLOGIC STUDIES IN A 6-YEAR-OLD BOY WITH HYPOGAMMAGLOBULINEMIA AND NODULAR LYMPHOID HYPERPLASIA TREATED WITH ENTERIC-COATED BUDESONIDE

Study	Value found in the patient	Normal for a 6-year-old
IgG, mg/dL	378	585–1,565
IgA, mg/dL	36	22–141
IgM, mg/dL	50	43–177
IgE, IU/mL	15	9–69
IgG-1, mg/dL	328	300–850
IgG-2, mg/dL	78	60–400
IgG-3, mg/dL	36	10–80
IgG-4, mg/dL	15.6	3–80
Anti-diphtheria, mcg/mL	0.41	≥0.05
Anti-tetanus, mcg/mL	0.97	≥0.50
Anti-HiB, mcg/mL	9.0	≥1.0
Anti- <i>Streptococcus pneumoniae</i> , mcg/mL	↓4/14 serotypes	≥70% of serotypes
ALC, cells/mm ³	2,645	1,900–3,700 ^a
CD3, %	65	60–76 ^a
CD4, %	28	31–47 ^a
CD8, %	35	18–35 ^a
CD19, %	7	13–27 ^a
CD19 + CD27+, %	14	25–40 ^b
CD19 + IgD-CD27+, %	5	≥6 ^b
CD56, %	10	4–17 ^a
PHA, %NR	54	≥50
Con A, %NR	94	≥50
PWM, %NR	82	≥50
<i>Candida albicans</i> , SI	2.8	≥3.0
Tetanus toxoid, SI	2.0	≥3.0

^aFrom Shearer et al.²⁷

^bFrom Alachkar et al.²⁸

Abbreviations: HiB, *Hemophilus influenzae* type b; ALC, absolute lymphocyte count; PHA, phytohemagglutinin; Con A, concanavalin A; PWM, pokeweed mitogen; %NR, percent normal response; SI, stimulation index; ↓, decreased.

abdominal pain and diarrhea persisted. At 7-years of age, endoscopy and colonoscopy were performed. Biopsies of the small intestinal and colon revealed increased number of enlarged lymphoid follicles. Barium swallow and small bowel follow through revealed “filling defects” principally in the ileum consistent with intestinal NLH. Plasma cytokines were measured by IBT Laboratories (Lenexa, KS) using a multiplex array format with the Meso Scale Discovery (MSD) Sector Imager 2400. MSD cytokine assays measure cytokines in a 96-well Multi-Spot plate. The assay employs a sandwich immunoassay format using electrochemiluminescence detection; a charge-coupled device (CCD) camera allows for the quantification of light emitted from each spot in each well. MSD software generates a standard curve to determine sample cytokine concentrations. As seen in Table 2, analysis of plasma inflammatory cytokines revealed elevated levels of interleukin (IL)-6, 25.2 pg/mL (normal <6.3 pg/mL), and IL-8, 9.0 pg/mL (normal <3.9 pg/mL). The patient was treated with oral enteric-coated budesonide (Entocort EC) 6 mg daily. After 2 months of oral budesonide treatment, the patient had improvement of the abdominal pain and decreased diarrhea and blood in the stool. The IL-6 level decreased to <6.3 pg/mL and the serum IL-8 level decreased to 2.8 pg/mL. After 6 months of oral enteric-coated budesonide treatment, the patient’s abdominal symptoms continued to im-

prove with decreased abdominal pain and firmer stools. The plasma IL-6 and IL-8 levels remained within normal limits, <6.3 pg/mL and 3.1 pg/mL, respectively.

Discussion

Several different types of immunodeficiency disorders have been seen in patients with NLH, but each shares the common feature of defects in the humoral limb of the immune system. The most frequently associated entity is common variable or late-onset hypogammaglobulinemia.^{1,6–8,11,12,14} In addition, selective IgA deficiency has been reported in patients with NLH of the small intestine.^{2,4,5,13} Slightly reduced IgG and IgA values and antibody deficiency to polysaccharide antigens have been reported in children with colonic NLH.^{14,17} This patient had decreased serum IgG levels, decreased memory and switched B cells, reduced IgG antibody titers to 28% of the *S. pneumoniae* serotypes, and decreased percentage of CD4+ T cells. Thus, he was classified as selective antibody deficiency with decreased IgG,^{18,19} though this may evolve into classic common variable immunodeficiency (CVID).

The immunopathogenesis of NLH is largely unknown. Hermans et al.¹ speculated that it might represent an aberrant response to repeated antigenic challenge in a host with an ineffective mucosal immune system. It is postulated that antigens stimulate the gastrointestinal lymphoid follicles, but because of ineffectiveness of the immune response, NLH develops. Supporting this hypothesis, Jacobson and deShazo observed abundant IgM-bearing lymphocytes in the intestinal lymphoid nodules of a child with selective IgA deficiency, suggesting that the increased cellularity represented a compensatory mechanism.⁵ The spectrum of gastrointestinal responses ranges from increased intraepithelial lymphocytes, NLH, to granulomatous enterocolitis.^{7,8,12,20} The nodules in NHL are principally in the lamina propria, superficial submucosa of the small intestines, but may also occur in the large intestine and rectum.^{7,20} These nodules contain large amounts of IgM+ B cells in addition to T cells and monocytes. It is speculated that increased numbers of IgM+ B cells may be attempted to compensate for IgA and IgG deficiencies. Mannon et al.²¹ examined cytokine synthesis of intestinal and colonic biopsies in patients with CVID and Crohn’s disease. As expected, tumor necrosis factor- α (TNF- α) synthesis was increased in Crohn’s disease but not CVID patients with increased intraepithelial lymphocytes. This is reminiscent of 2 different pulmonary diseases of lymphoid interstitial pneumonitis (LIP) and granulomatous interstitial

TABLE 2. PLASMA INFLAMMATORY CYTOKINES IN A 6-YEAR-OLD BOY WITH HYPOGAMMAGLOBULINEMIA AND NODULAR LYMPHOID HYPERPLASIA TREATED WITH ENTERIC-COATED BUDESONIDE

Study	Time of budesonide treatment			Normal ^a
	0 months	3 months	7 months	
IL-1b, pg/mL	<0.6	<0.6	<0.6	<1.1
IL-6, pg/mL	25.2	<6.3	<6.3	<6.3
IL-8, pg/mL	9.0	2.8	3.1	<3.9
TNF- α , pg/mL	3.2	5.0	4.1	<5.3

^aIBT Laboratories.

Abbreviations: IL, interleukin; TNF- α , tumor necrosis factor- α .

lung disease (GILD) seen in patients with CVID.²² In the former, there are diffuse infiltrates of lymphoid tissue and consisting of B cells, T cells, and histiocytes. In addition, germinal centers may be seen. In GILD, the histopathology demonstrates loose clusters of epithelioid histiocytes, multinucleated giant cells, and lymphocytes. In patients with GILD, TNF- α levels are elevated and have been treated successfully with anti-TNF therapy, infliximab.²³ In our patient, TNF- α levels were not elevated consistent with the lack of granulomata formation. However, plasma IL-6 levels were greatly increased. IL-6, previously called B cell differentiation factor, stimulates B cells causing switch for IgG-1 and IgA secretion and a differentiation factor for plasma cells. Plasma IL-8 levels were also modestly increased. IL-8 is a chemokine, principally for neutrophils. Thus, the pattern of increased IL-6 and not TNF- α is consistent with the histopathology seen in NLH.

Treatment for NLH associated with immunodeficiency has been largely unsatisfactory. Eradication of *G. lamblia* infestation, often present in this condition, may improve the chronic or recurrent diarrhea but has not altered the radiographic appearance of NLH. Similarly, immunoglobulin replacement therapy has sometimes resulted in amelioration of the diarrhea but has not improved the radiographic appearance or histopathology of NLH. Chua et al.²⁴ treated successfully 3 patients with infliximab who had CVID and severe enteropathy. The patients had villous atrophy; thus, it resembled the sprue-like enteropathy seen in CVID.

LIP typically responds with systemic corticosteroids.²² Given the histopathologic similarities of LIP and NLH, we proposed that NLH would respond to corticosteroids. Corticosteroids suppress T cell and macrophage cellular immune responses and B cell humoral responses. Interestingly, patients with Crohn's disease involving the terminal ileum have been treated with oral budesonide successfully.²⁵ Budesonide is a potent corticosteroid designed to have location-specific delivery to the gastrointestinal tract and has limited systemic bioavailability. Thus, budesonide would be a safer alternative to systemic corticosteroids. We postulated that budesonide would have mucosal anti-inflammatory effects, as it does in the treatment of asthma. *In vitro* studies have demonstrated that budesonide downregulates the production of NF- κ B and inflammatory cytokines IL-1, IL-6, and TNF- α .²⁵ However, it was not certain that budesonide would be effective in treating NLH. In NHL, Elnachef et al.²⁶ recently described a 47-year-old woman who had CVID. The NHL was present in the mid and terminal ileum, similar to our patient. She was treated with oral enteric-coated budesonide, and the diarrhea, abdominal pain, and bloating improved over ~3 months. Our patient also improved after starting enteric-coated budesonide over a similar period. In addition, elevated plasma IL-6 and IL-8 levels lowered to normal values. This suggested that the oral budesonide does have anti-inflammatory effects in NHL. Future studies should examine small intestinal mucosa inflammatory cytokines to determine whether there is correlation with plasma inflammatory cytokines.

In summary, we report a 6 year-old boy with hypogammaglobulinemia and NLH. The NLH was associated with elevated plasma IL-6 and IL-8. After treatment with oral enteric-coated budesonide, the plasma IL-6 and IL-8 levels became undetectable, and the patient's diarrhea and abdominal pain improved.

Author Disclosure Statement

No competing financial interests exist.

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