Primary Intestinal Lymphangiectasia as a Cause of Combined Immunodeficiency

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Introduction

Primary Intestinal Lymphangiectasia (PIL), also known as Waldmann's disease, is a rare disorder characterized by markedly dilated intestinal lymphatic vessels. The dilation, sometimes even rupture, of the lymphatic vessels causes the leakage of lymph through the gastrointestinal tract. This leakage then can cause hypoproteinemia, hypogammaglobulinemia, and lymphopenia. Although the disorder is frequently framed in gastrointestinal terms, the hallmark lymphatic leakage also results in profound immunodeficiency.

Case Description

An eleven-year-old male had an unremarkable past medical history until the development of a recurrent *Cryptosporidium* infection. The patient experienced chronic diarrhea, abdominal bloating, intermittent emesis, and generalized, non-radiating pain occurring ~4 times a week. He had mild abdominal distention and positive fluid thrill. Initial laboratory investigations revealed leukocytosis, thrombocytosis, hypoalbuminemia, and hypoproteinemia, along with a mildly elevated fecal calprotectin. Abdominal ultrasound demonstrated marked bowel wall thickening, and CT of the abdomen and pelvis showed diffuse enterocolitis, mesenteric lymphadenopathy, ascites, and bilateral pleural effusions. Immunophenotyping revealed combined immunodeficiency, characterized by severe hypogammaglobulinemia (total IgG: 212 mg/dL) and significant T cell lymphopenia (CD4+ count: 172 cells/μL; CD8+ count: 208 cells/μL). Genetic evaluation, including a comprehensive primary immunodeficiency panel and whole exome sequencing, identified a heterozygous pathogenic deletion of exons 2-4 in the ADA2 gene. While this gene is associated with deficiency of adenosine deaminase 2 (DADA2), the disorder follows an autosomal recessive inheritance pattern, and a heterozygous variant would not be expected to be disease-causing. Furthermore, the peripheral blood ADA2 level was determined to be normal.

Total WBC	**5.32**	K cells/ μL
Total Hgb	**14.1**	g/ dL
Total Plt	**329**	K cells/ μL
ALC	**0.88**	K cells/ μL
ANC	**3.66**	K cells/ μL
Total CD3⁺ T cells	**415**	cells/ μL
Total CD4⁺ T cells	**172**	cells/ μL
Total CD8+ T cells	**208**	cells/ μL
Naïve CD4⁺ T Cells	**15.3**	cells/ μL
Eff. Mem. CD4⁺ Cells	**40.8**	cells/ μL
Cen. Mem. CD4⁺ Cells	**41.6**	cells/ μL
Total IgG	**212**	mg/ dL
Total IgA	**40**	mg/ dL
Total IgM	**46**	mg/ dL
Total IgE	**102**	unit/ mL

Table 1: Initial immune laboratory results obtained prior to the initiation of any immunomodulatory treatment. Values in blue are low while those in red are elevated.

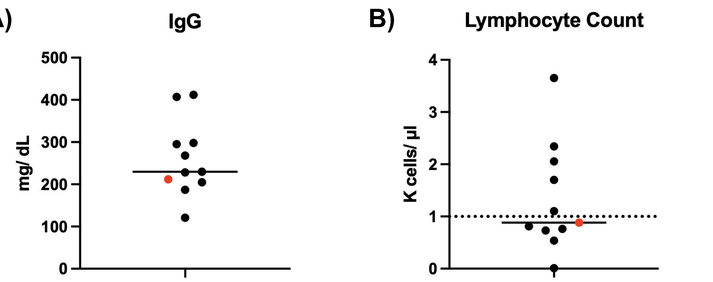

Figure 1: Comparison of IgG levels (A) and lymphocyte count (B) between our patient (red dot) and 10 previously reported cases (black dots) from the literature. For B, the dotted line indicates the lower limit of the normal lymphocyte range.

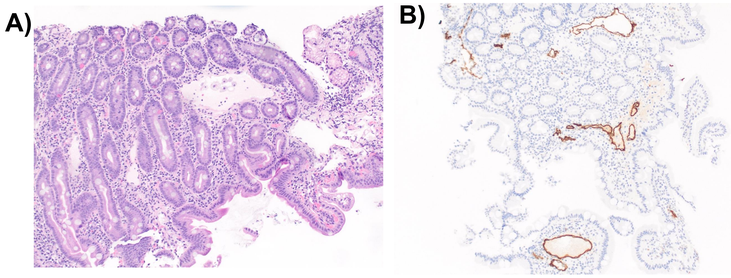

Figure 2: Dilated lymphatics observed in the lamina propria from EGD biopsy samples. A) Hematoxylin and eosin (H&E), 100x magnification: dilated lymphatics appear as "empty spaces" within the lamina propria. B) D2-D40 immunostain, 100x magnification: dilated lymphatics are highlighted in brown, confirming lymphatic identity.

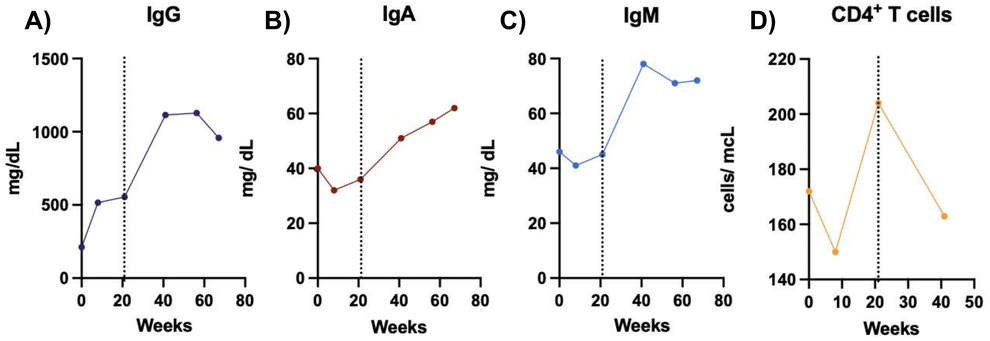

Figure 3: Patient's IgG, IgA, IgM, and CD4⁺ T cell levels over time. The dotted line represents when the dietary intervention was initiated.

Case Continued

Unresolved symptoms led the patient to be re-evaluated for protein-losing enteropathy, and stool studies again showed markers of intestinal inflammation. An esophagogastroduodenoscopy (EGD) with duodenal biopsies confirmed the diagnosis of PIL. Following diagnosis, a targeted nutritional regimen was initiated. This included a strict low-fat diet (12 grams per day), high-protein intake (75–125 grams per day), supplementation with fat-soluble vitamins (A, D, E, K), and daily medium-chain triglyceride oil. At follow-up after diet initiation, the patient reported significant clinical improvement. He experienced only 1–2 episodes of diarrhea per month, with resolution of bloating, abdominal pain, nausea, vomiting, and peripheral swelling. Immunologically, his total IgG level increased to 1114 mg/dL, although his T cell lymphopenia remained unchanged (Figure 3A & 3D).

Comparison to Literature

As seen in Figure 1, our patient's laboratory values fell approximately at the median when compared to other reported cases. Dietary intervention was effective in this case; however, it is important to note that, based on the literature, dietary management tends to be most successful in pediatric patients. Adults or those diagnosed later in life may require additional or alternative therapeutic approaches. Overall, intestinal lymphangiectasia should be recognized as a non-hematopoietic cause of combined immunodeficiency and considered in the differential diagnosis of such presentations.

Acknowledgements

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