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LETTER TO EDITOR

A Clinical Approach to a Child with Hypoalbuminemia and Lymphopenia

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To the Editor,

Primary immunodeficiency diseases (PIDs) are a genetically heterogeneous group of disorders affecting distinct components of the immune system. The initial approach to a suspected PID patient includes analysis of leukocyte subgroups and functions. Lymphopenia is a crucial marker for PIDs, especially for T cell deficiencies such as severe combined immune deficiency (SCID). However complete evaluation of a patient is critical for correct diagnosis.

Primary intestinal lymphangiectasia (PIL) is a rare and important cause of secondary lymphopenia caused by congenital malformation of intestinal lymphatic drainage leading to protein-losing gastroenteropathy [1]. Due to protein leakage edema is the major clinical presentation, accompanied by lymphopenia, hypoalbuminemia and hypogammaglobulinemia.

This report introduces a case of PIL with CMV infection in a 2 month-old male patient. Despite PIL cases are associated with both humoral and cellular immune abnormalities; opportunistic infections are not so common as seen in immunocompromized patients [1]. Here, we report a PIL presenting with both neutropenia and lymphopenia, resulting in CMV infection.

A 2-month-old boy, born out of non-consanguineous marriage, was admitted to hospital with 3-day history of watery diarrhea and fever. His diarrhea started three days before, was watery and mucoid. He was fed with breast-milk and formula. On physical examination vitals were normal, weight, height and head circumference were appropriate for his age (weight gain + 30 g/kg/day). He had slight pitting edema of his lower limbs and eyes, and bilateral hydrocele, no dysmorphy was observed. Steatorrhea was detected; however blood, parasites, reductant substances rotavirus and adenovirus antigens were negative in the stool samples and culture showed no pathogens. On admission, laboratory findings were as follows: total protein 2.4 g/dL, albumin 1.4 g/dL, serum calcium 1.26 mmol/L, magnesium 0.46 mmol/L, fibrinogen 1.6 g/L and immunoglobulins were low according to age referrals. Biochemical parameters were otherwise normal. On complete blood count analysis absolute neutrophil and lymphocyte counts were 790 and 2500/mm^3 respectively (Table 1). Alpha1-antitrypsin level in the stool was normal. 24-h urine protein loss was normal. The sweat chloride concentrations of the patient were 21 mM/L (normal: <40 mM/L). Cow's milk protein allergy was excluded. Peripheral blood lymphocyte subgroups analysis revealed T-cell lymphopenia, with a prominent decrease in CD4+CD45RA+ naïve T-cells. CD4+ CD45RA+CD31+ T cells representing T-cell receptor excision circles (Trec) were low (<50 %), however thymus was visualized on chest X-Ray (Supplement Fig. 1). Lymphocyte activations were normal with phytohemaglutinin and anti-CD3 stimulation. Despite B cell counts were within age referrals, profound hypogammaglobulinemia persisted. Switched memory and marginal zone B cells were detected low according to EUROClass age referrals for B lymphocyte subsets. Intravenous immunoglobulin (IVIG) replacement and

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Table 1 Immune system parameters of the patient before and after MCT formula replacement

	On admission	After MCT formula	Age references
Hb (g/dL)	13.3	12.6	10.5–14
Absolute lymphocyte count (/mm^3)	2500	7920	>3000
Absolute neutrophil count (/mm^3)	790	2920	>3000
Thrombocyte (/mm^3)	245,000	494,000	150,000–450,000
Albumin (g/dL)	1.4	4.4	3.2–4.8
IgA (mg/dL)	9.3	19.7[a]	7–123
IgG (mg/dL)	140	755[a]	304–1231
IgM (mg/dL)	19.8	40[a]	32–203
CD3+CD16-56- (%)	36	55	51–79
CD3-CD16+56+ (%)	32	17	5–23
CD3+CD4+ (%)	17	32	31–54
CD3+CD8+ (%)	15	19	10–31
CD19+ (%)	29	23	14–44
CD20+ (%)	29	23	13–40
CD4+CD45RO+ (%)	8	9	6–21
CD4+CD45RA+ (%)	7	26	25–45
CD4+CD45RA+CD31+ (%)	17	52	>50
Activation by PHA			
CD3+CD25+ (%)	50	52	52–94
CD3+CD69+ (%)	52	44	48–85
Switched memory B cells (%)	2.9	4.2	6.5–29.2
Marginal zone B cells (%)	2.8	2.8	7.2–30.8
Naïve B (%)	97.0	90.5	59.8–85.8
Activated B cells (%)	2.7	1.9	1.1–6.9

[a] Six weeks after cessation of IVIG replacement

trimethoprim-sulfamethoxazole prophylaxis was initiated. Cytomegalovirus (CMV) PCR was 690 copy/mL; CMV IgM was positive whereas IgG was negative. The CMV status of the mother before or during the pregnancy was not known; but no exanthematous disease was noted on her pregnancy records. She was negative for CMV IgM, but IgG was positive. Ganciclovir (10 mg/kg/day) was started. Ganciclovir treatment was continued for 2 weeks, after which PCR copy numbers were below detection limits and ganciclovir was stopped. Since the patient had persistent neutropenia together with intermittent diarrhea, he was evaluated for Shwachman Diamond Syndrome (SDS). Pancreas was visualized under ultrasound, stool fecal elastase enzyme level and extremity X-Rays were normal; so SDS was excluded. During the hospitalization period, neutropenia alleviated (absolute neutrophil count: 1400/mm^3) and lymphopenia became prominent (absolute lymphocyte count: 900/mm^3). Upper intestinal endoscopy showed only edema but otherwise, was normal. Duodenal histology demonstrated normal looking villi with normal villous/crypt ratio. No intraepithelial lymphocytosis or lamina inflammation was observed (Supplement Fig. 2). There were, however; individual villi, which showed dilated lacteal-like lymphatics causing villous blunting (Supplement Fig. 3). Esophageal and gastric mucosae appeared histologically normal. Ultrasound examination of the heart and abdomen excluded secondary causes of lymphangiectasia. The final diagnosis was PIL. Breastfeeding was continued and a formula with a high concentration of medium chain triglycerides (MCT) was introduced which resulted in rapid clinical improvement after 4 weeks. Serum albumin level increased remarkably and; edema regressed and the infant gained weight. Six weeks after the last dose of IVIG, immunglobulins were within age referrals; together with normal T cell counts and Trec (Table 1). No CMV flare up was detected after the ganciclovir treatment.

Lymphopenia and hypogammaglobulinemia are definite indicators of severe PIDs such as SCID, however functional studies are of crucial importance for differential diagnosis [2]. In the current case, the presence of thymus and normal lymphocyte functions had driven us away from primary to secondary causes of immune deficiencies.

Presence of lymphopenia together with hypogama globulinemia, hypoalbuminemia, edema and steatorrhea led us to consider PIL in the first line. PIL is a congenital disorder of the lymphatic system characterized by dilated and tortuous intestinal lymphatics resulting from obstructed lymphatic

drainage. PIL is primarily affecting children and young adults [3]. Although most cases are sporadic, PIL has been reported in multiple siblings of several families, suggesting that at least in certain cases it may have a genetic etiology. Generalized lymphangiectasia with variable intellectual disability and characteristic dysmorphic features (such as facial flattening, broad nasal bridge and hypertelorism) is defined as Hennekam syndrome. It is an autosomal recessive disorder caused by the mutations in CCBE1 gene. Recently, it has been suggested that all patients, even lacking characteristic features of Hennekam syndrome, with unexplained lymphangiectasia should be considered for CCBE1 mutation analysis [4].

The most common symptoms of patients with PIL include intermittent diarrhea, nausea and vomiting. Some patients have mild to moderate steatorrhea. Peripheral edema is often present, pitting type and usually symmetrical in distribution involving lower limb and sometimes severe edema on face, scrotum or vagina. Chylous pleural effusions (chylothorax) and chylous ascites may be present. Growth is retarded if onset is in the first decade of life [5].

Diagnosis is confirmed by endoscopy and small bowel biopsy. Endoscopy of the upper intestinal tract is crucial in establishing the diagnosis, during which white opaque spots may be detected on the duodenal mucosa and characteristic "snow flake appearance" of the duodenum may be seen. Definitive diagnosis is made by biopsies sampled during endoscopy, which show dilated lymphatic channels. Because the mucosal lesions in PIL are often patchy and localized, endoscopy is used to selecting regions for biopsy. Differently, multiple mucosal biopsies may be necessary if peroral jejunal sampling is used [3, 5]. In our case, interestingly, the endoscopic appearance of bulbus and duodenum was normal, except for duodenal edema; and the diagnosis was confirmed with characteristic histological findings.

Lymphangiectasia can occur in any area of the body; in the intestine, the impaired lymphatic drainage leads to leakage of protein-rich chyle into the intestinal lumen, causing protein-losing enteropathy, hypoalbuminemia and peripheral or edema [5]. Lymphopenia is common and indicates the failure of lymphocytes in the lymphatics to return to the general circulation due to the structural changes. Immunological disorders involving both T- and B-cell lineages are encountered. Low immunoglobulin levels indicate for B cell defect. T cell defect is characterized by lymphopenia, specifically low counts for T-helper series and CD4+CD45RA+ naïve T cells were reported. Reduction in T cell counts, may either be caused by diminished production or increased loss by peripheral destruction and sequestration [6, 7]. Although intestinal leakage was thought to be the main cause of T cell depletion, recently other mechanisms have been hypothesized for selective T cell loss. Sequestration of naïve T cells into lymphoedematous tissue and increased peripheral apoptosis indicated by increased Fas/CD95 receptors on CD4+ T cells were previously reported [6, 7]. No evidence was found for depletion of thymic production. In our patient CD4+CD45RA+ T cells were low consistent with previous data; however Trec were low, which led us to consider diminished production by thymus. We also showed that switched memory and marginal zone B cells were low, which may have led to defective antibody production. T cell lymphopenia reversed with MCT replacement.

Regardless of the cellular and humoral immune defects, PIL patients do not encounter with severe opportunistic infections as seen in immunocompromized patients. However, antimicrobial prophylaxis is suggested for these patients to control morbidity and mortality of infections [7]. To date, cryptococcal infections were reported together with bacterial pathogens such as *Klebsiella* and *Streptoccus* [6–8]. CMV infection leading to secondary intestinal lymphangiectasia was described before [9], however our patient is the first one reported with CMV infection in PIL. The active CMV infection presumably contributed to atypical presentation with neutropenia. Although we did not have the previous CMV serology of his mother, it might have been a perinatal or postnatal via breastfeeding transmission. He responded well to ganciclovir, and no recurrence of CMV infection was detected.

Because of the rarity of PIL, there are no long-term randomized, controlled studies existing to guide treatment. Experience in treating PIL has been derived mostly from case reports and small case series. One of the simplest and most widely used treatments is dietary modification, with replacement of fat with MCT, fat-free and a high-protein diet. Because MCTs are absorbed rapidly by the intestinal mucosa and can be metabolized and excreted directly into the portal venous system rather than via intestinal lacteals, there is a reduced load on the damaged lymphatic system. Our patient responded well to MCT replacement, with full recovery of gastrointestinal and immunological parameters. Lifetime follow-up is indicated in PIL patients because of the risk of relapsing clinic and lymphoma development [10].

In conclusion, PIL is known to be associated with some immune abnormalities without causing severe opportunistic infections. However the existence of PIL and CMV infection in the same infant as in our case may cause confusion in the diagnosis. MCT replacement in the diet is observed to be highly effective, with improvement in clinical symptoms of PIL as well as abnormal laboratory values including immune abnormalities.

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