www.jcimcr.org

JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Case Report

Open Access, Volume 6

Protein Losing Enteropathy (PLE) secondary to Norovirus infection in an immunocompetent 4-year-old patient: Case report and literature review

Sadhana Durbha BA[1]; Edward Xie BA[1]; Haylee Sprangers[1,2]; Katherine Mahoney[5]; Janelle McGill[1,2,3]; Ingrid Camelo[1,2,3,4]*

[1]Medical College of Georgia, Augusta University, USA.

[2]Pediatrics Department, Augusta University, USA.

[3]Children's Hospital of Georgia/Wellstar, USA.

[4] Pediatric Infectious Diseases Deparment, Augusta University, USA.

[5] Pediatrics Department, Washington University School of Medicine, USA.

***Corresponding Author: Ingrid Y Camelo**

Associate Professor, Children's Hospital of Georgia, Medical College of Georgia, Augusta University Section of Pediatric Infectious Diseases, Augusta, GA, USA.

Phone: 706-721-4760, Fax: 706-721-3295;

Email: icamelo@gmail.com

Received: Feb 12, 2025

Accepted: Mar 18, 2025

Published: Mar 25, 2025

Archived: www.jcimcr.org

Copyright: © Camelo IY (2025).

DOI: www.doi.org/10.52768/2766-7820/3524

Keywords: Protein Losing Enteropathy (PLE); Norovirus; Infection; Immunocompetent; Children.

Abstract

In Protein-losing enteropathy (PLE), proteins are lost from the gastrointestinal system exceeding their synthesis by other organs. Proteins entering the gut are degraded into amino acids and reabsorbed but conditions causing inflammation or erosion of the gastrointestinal tract increase mucosal permeability with excessive leakage and poor reabsorption. Clinical manifestations include edema due to decreased plasma oncotic pressure, ascites, and pleural effusions. Loss of immunoglobulins and lymphocytes predisposes to infection. Laboratory findings include hypoproteinemia, low serum globulins and Alpha 1 antitrypsin (A1AT) abnormal intestinal clearance [1] PLE precipitated by Norovirus infection has been described in immunocompromised pediatric patients but not in those immunocompetent. Here, we discuss a case of PLE precipitated by Norovirus in a immunocompetent 4-year-old patient. Treatment included intravenous (IV) fluids, furosemide and albumin. Along with a case description, we provide a summary of prior pediatrics PLE case reports from other causes as well as from Norovirus in immunocompromised patients. This case emphasizes the importance of recognizing the wide variety of etiologies for PLE, both established and novel. It also highlights the importance of recognizing PLE as a condition occurring in immunocompetent patients to prevent delays in diagnosis and treatment initiation, unnecessary testing, or increased length of hospital stay.

Introduction

PLE is a condition precipitated by multiple factors, whereby serum proteins leak into the intestinal tract and are lost faster than they are produced endogenously or reabsorbed via lymphatic flow [2]. Due to hypoproteinemia, fluid is more likely to leak out of vessels resulting in clinical manifestations predominantly diffuse edema, abdominal distension and diarrhea. Laboratory evidence include hypoproteinemia, leukocytosis, elevated acute inflammatory markers, and transaminitis. Radiological evidence shows pleural effusions or ascites. Generally, hypoproteinemia secondary to PLE is nonspecific and results in acute hypoalbuminemia and hypogammaglobulinemia. The gold standard for diagnosis of PLE includes obtaining a 24-hour alpha-l-antitrypsin (A1AT) fecal excretion rate, abnormal clearance is precipitated by gastrointestinal loss [3]. PLE in pediatric populations has previously been associated with autoimmune

conditions such as Crohn's Disease and gastrointestinal sarcoidosis [4-8]. However, to our knowledge, this is the first documented case of PLE occurring secondary to Norovirus infection in an immunocompetent pediatric patient.

Case presentation

A 4-year-old male with no significant past medical history was referred to our institution with complaints of severe abdominal pain, vomiting, decreased oral intake of 2 days duration, constipation followed by non-bloody diarrhea, dyspnea, and edema in his genital area and lower extremities. His mother noted that his symptoms started shortly after he was exposed to his grandmother who was previously diagnosed with a gastrointestinal illness. A computer tomography (CT) scan of the abdomen showed diffuse ascites and a borderline enlarged appendix prompting a transfer for further management.

On arrival at our institution, vital signs included a temperature of 37 (C), heart rate of 139 beats per minute, respiratory rate of 28 breaths/min, blood pressure of 102/64 mmHg, O_2 saturation of 96% on room air. Upon physical exam, he was alert. A cardiopulmonary examination revealed diminished breath sounds in the left and right lower bases. Abdominal exam was notable for a diffusely tender abdomen, particularly below the umbilicus with guarding and dullness to percussion. Additionally, the patient had scrotal and pedal edema. On laboratory examination, White blood cells (WBC) 28 th/mm^3 (RR 4.5-49.9), Sodium 127 mEq/L (RR 132-146), potassium 4.8 mEq/L (RR 3.5-5.5), chloride 95 mEq/L (RR 99-109), Co2 17 mEq/L (RR 20-31), BUN 29mg/dL (RR 9-23), creatinine 0.35 mg/dL (RR 0.50-0.80), Aspartate aminotransferase (AST) 78 units/L (RR 11-35), Alanine aminotransferase (ALT) 25 units/L (RR 10-49), gamma-glutamyl transferase (GGT) 3 units/L (RR 8-50), albumin 2.8 g/dL, RR (3.2-4.8 g/dL), IgA level 104 mg/dl (RR 29-256), IgG level 367 mg/dL (RR 386-1470) and IgM level 27 mg/dL, (RR (37-224). On two different sample collections the same day, our patient had 236 mL of stool excretion. A random fecal A1AT of 30 mg/dl (RR <56) was used as a surrogate for the 24 hour collection. Serum A1AT was 235.5 mg/dL, RR (100-190 mg/dL). The normal clearance of A1AT should be under 13 ml/24 hours. A clearance greater than 27 ml/ day indicates increased gastrointestinal protein loss and points towards the diagnosis of PLE, the calculated A1AT clearance for him was consistent with PLE. A1A Clearance (c) = (stool volume (cc)) x A1A random fecal concentration (mg/dL)/ serum A1AT (mg/dL), A1A(c) = 236 ml x 30 mg/dl / 235.5 mg/dl. A1A(c) = 30 ml/day [3]. Further testing included negative Antinuclear antibodies, normal Tissue Transglutaminase IgA antibody (tTG-IgA), T cell CD4 726 cells/ mcl (RR 700-2200)/22% (RR28-47), CD8 836 cells/mcL (RR 480-1300), Cytomegalovirus (CMV) IgM negative, Epstein-Barr Virus (EBV) serology negative for acute infection, a BioFire® FilmArray® gastrointestinal (GI) Polymerase chain reaction (PCR) panel was negative for Campylobacter, Plesiomonas shigelloides, Salmonella, Vibrio cholerae, Yersinia enterocolitica, Enteroaggregative E. coli (EAEC), Enteropathogenic E. coli (EPEC), Enterotoxigenic E. coli (ETEC), Shiga-like toxin-producing E. coli (STEC), E. coli 0157, Enteroinvasive E. coli (EIEC), Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica, Giardia lamblia, Adenovirus, Astrovirus, Rotavirus and Sapovirus but positive for Norovirus. A respiratory Biofire® FilmArray® PCR panel was negative for Sars-CoV-2, Influenza A and B virus, Metapneumovirus, Parainfluenza, Respiratory Syncytial Virus (RSV), Bordetella, pertussis, Chlamydia pneumoniae, Mycoplasma pneumoniae, and Bordetella parapertussis. A chest x-ray (CXR) was notable for pleural effusion at the right lung base with mild linear opacities likely indicative of compressive atelectasis.

Based on this patient's initial complaints of severe diarrhea and diffuse swelling, laboratory evidence of hypoproteinemia and hypoalbuminemia, radiological evidence of ascites and pleural effusions, abnormal A1AT clearance, and a positive GI PCR panel for norovirus, this patient was diagnosed with PLE most likely precipitated by Norovirus infection. Treatment included intermittent oxygen therapy via nasal cannula in order to keep oxygen levels above 92% and repeated albumin replacement infusion along with furosemide administration to manage fluid overload. A follow-up CXR showed interval improvement in the pleural effusions. Abdominal and scrotal edema as well as pleural effusions improved from initial values 11 days after admission and 7 days after initiating albumin and diuretics. IgG and IgM levels improved to 661 mg/dL and 46 mg/dL respectively. Furosemide and albumin were ultimately discontinued, and the patient was discharged home in stable condition and on room air.

Discussion/conclusion

This is the first case to our knowledge of protein-losing enteropathy secondary to norovirus infection in an immunocompetent pediatric patient. There have been several cases of PLE secondary to norovirus in immunocompromised pediatric patients as well as secondary to several other conditions, outlined in the Table 1. Key findings in this patient indicative of PLE included diarrhea and generalized edema, as well as laboratory findings including hypoalbuminemia, hyponatremia, pleural effusions on CXR, both of which were managed with diuretics, albumin, supplemental oxygen, and supportive care, similar to treatment received by other children diagnosed with the same condition. While conducting this review, we found 13 manuscripts that linked infectious etiologies to PLE including cytomegalovirus (CMV), Human immunodeficiency virus (HIV), and SARS-CoV-2 [4-7,9,10]. We also found a study that linked Norovirus to PLE in an immunocompromised patient [11]. Given the frequency of Norovirus in children and prior reports of its association with PLE development, Norovirus should be considered as a precipitating factor for the development of PLE in patients with diarrhea in addition to fluid retention even when if the patient is immunocompetent.

Norovirus has long been recognized as a leading cause of viral gastroenteritis worldwide. To clear norovirus, CD8+ and CD4+ mediated responses are necessary. Symptoms of norovirus include diarrhea and vomiting [12]. Severe diarrhea caused by norovirus can lead to the elimination of proteins from the GI tract faster than they are produced, therefore resulting in hypoproteinemia, a defining feature of PLE. Leukocytosis, anemia, and transaminitis are also commonly seen [3]. Additionally, a normal rate of A1AT clearance is below 13 mL/day, with a clearance over 27 mL/day raising suspicion for PLE. Because our patient's A1AT clearance rate was above 27 mL/day, this indicated a PLE diagnosis [3]. In immunocompetent patients with

Table 1: Immunocompetent patients' cases.

Immunocompetent patients' cases					
Study	**Age/sex**	**Clinical presentation**	**Associated infectious organisms**	**Proposed pathogenesis of PLE**	**Treatment**
Akkelle et al, 2018 [14]	13 month/M	Watery diarrhea, vomiting, swelling of face and abdomen	*Giardia lamblia*	Damage to the intestinal mucosa and impairment of the enterocyte barrier function	Albumin metronidazole
	14 month/F	Diarrhea, facial swelling, distended abdomen			
	19 month/M	Vomiting, diarrhea, abdominal swelling			
Ferreira et al, 2021 [15]	7 month/M	Fever, watery diarrhea, severe anasarca	*Yersinia enterocolitica* colitis complicated by *Kodomaea ohmeri* sepsis	None described	Albumin Multiple antibiotics and antifungals Enteral feeding supplemented with parenteral feeding
Rohani et al, 2021 [7]	6 year/M	Severe RLQ abdominal pain, fever, diarrhea, vomiting	COVID-19 and Necrotizing enterocolitis	None described	Parenteral nutrition Broad-spectrum antibiotics
Parisi et al, 2018 [6]	6 month/F	Diarrea, fever, generalized edema	Rotavirus	Intestinal mucosal injury causing enhanced permeability	Corticosteroids Unspecified antibiotics Correction of fluids and electrolytes Albumin
Iwasa and Matsubayashi, 2008 [16]	6 month/M	Vomiting, diarrhea, dehydration, peripheral edema, abdominal distention, hypoactive bowel sounds	Rotavirus	Enhanced vascular permeability due to intestinal mucosal damage by rotavirus	Hyperalimentation Albumin IVIG Dexamethasone
Iwanaga et al, 2003 [9]	6 week/F	Watery diarrhea, failure to thrive, lethargy, facial pallor, peripheral edema	CMV	None described	Ganciclovir IVIG Hyperalimentation
Hoshina et al, 2009 [17]	8 year/M	Nausea, peripheral edema, ascites	CMV	Lymphangiectasia at terminal ileum	None described
Russo et al, 2012 [18]	11 year/M	Epigastric pain, vomiting, transient diarrhea, peripheral edema	CMV	Hypertrophic gastropathy	Albumin Omeprazole Sucralfate High-protein diet
Immunocompromised patients' cases					
Cakir et al, 2015 [4]	15 year/F	Abdominal pain, abdominal distension, lower extremity edema, watery diarrhea, mucocutaneous pallor, ascites	CMV colitis and Crohn's Disease	Leakage of protein-rich fluids across the eroded epithelium due to CMV or Crohn's	Unspecified antibiotics Albumin Parenteral nutrition IVIG Mesalamine Prednisolone
Cobos-Carrascosa et al, 2015 [5]	13 year/M	Peripheral edema, abdominal discomfort	HIV on ART, *Mycobacterium genavense*	Intestinal lymphangiectasia causing chronic obstruction leading to excessive intraluminal intestinal pressure	Albumin IVIG
van de Ven et al, 2011 [11]	14 year/M	Chronic diarrhea, nausea, abdominal pain	CVID, Human parechovirus type 1 (HPeV), Norovirus	Perpetuated immune-mediated inflammatory infiltration of the intestines (autoimmune enteropathy)	IVIG Parenteral nutrition Lactoferrin Immunosuppressive therapy (prednisone, tacrolimus, pleconaril)

Xi et al, 2022 [19]	14 year/M	Diarrhea, peripheral edema, gross hematuria	Tuberculosis	Increased venous and hydrostatic pressure leading to impaired lymphatic drainage	Albumin Captopril, dipyridamole Pericardiectomy
Nakamura et al, 2010 [20]	5 year/M	Abdominal pain, vomiting, bloody stool, purpura	Streptococcal infection Henoch-Schönlein purpura	Vasculitis causing increased capillary permeability or submucosal hemorrhage and ulceration	Prednisolone Dalteparin Ulinastatin Factor XIII (only for 4 year/M patient with low Factor XIII activity)
	4 year/M	Colicky abdominal pain, low grade fever, vomiting, bloody stool, purpura, peripheral edema	Henoch-Schönlein purpura		

*CMV: Cytomegalovirus; IVIG: Intravenous Immunoglobulin; HIV: Human Immunodeficiency Virus; ART: Anti-Retroviral Therapy; CVID: Common Variable Immunodeficiency; PLE: Protein Losing Enteropathy.

intact CD8+ and CD4+ mediated response, it may be less common for gastrointestinal infections such as Norovirus to cause clinical manifestations of PLE. However, this case highlights the importance of recognizing Norovirus as an etiology of PLE in immunocompetent patients.

Our literature review performed via PubMed search (summarized in Table 1) shows several cases of PLE in pediatric patients linked to infectious causes, including both immunocompetent and immunocompromised hosts. Since this patient was immunocompetent, consideration was not initially given to Norovirus as the primary etiology of PLE, which could have eliminated the need for further workup. Consequently, recognizing Norovirus as a possible etiology of PLE in pediatric patients, can prevent delays in diagnosis and management and avoid unnecessary testing.

This case presents a patient with PLE secondary to Norovirus infection, which had not been previously documented as a trigger for PLE in immunocompetent pediatric patients. This patient's treatment course was delayed due to not including PLE in the initial differential diagnosis, resulting in an inability to promptly analyze the gold standard diagnostic testing, calculation of 24-hour alpha-1-antitrypsin fecal excretion rate [13]. This case thus highlights the importance of recognizing infections outside of the historically recognized etiologies of PLE to avoid delayed diagnosis, unnecessary testing, prolonged hospitalizations, and delays in treatment. Further, it is important to recognize PLE as a condition that can occur in immunocompetent pediatric patients.

Acknowledgements: Sadhabna Durbha, Edward Xie and Haylee Sprangers conducted the data gathering and literature review, Janelle McGill and Katherine Mahoney contributed by critically revising the manuscript. Ingrid Camelo provided intellectual content in infectious diseases, provided editing and final approval for submission (TABLE 1). Summary of Pediatric cases of Protein Losing Enteropathy (PLE) associated with infectious diseases in immunocompetent and immunocompromised patients.

References

1. Ozen A, Lenardo MJ. Protein-Losing Enteropathy. New England Journal of Medicine. 2023; 389(8): 733-748. doi:10.1056/NEJMra2301594
2. Levitt DG, Levitt MD. Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states. Clinical and Experimental Gastroenterology. 2017/07/17. 2017; 10(null): 147-168. doi:10.2147/CEG.S136803
3. Nagra N, Dang S. Protein-Losing Enteropathy. January 2023. StatPearls
4. Cakir M, Ersoz S, Akbulut UE. Disseminated cytomegalovirus infection and protein losing enteropathy as presenting feature of pediatric patient with Crohn's disease. Pediatr Gastroenterol Hepatol Nutr. 2015; 18(1): 60-5. doi:10.5223/pghn.2015.18.1.60
5. Cobos-Carrascosa E, Martin-Nalda A, Alvarez M, Segarra O, Frick MA, Soler-Palacin P. Protein-losing enteropathy in an HIV-infected pediatric patient with previous disseminated Mycobacterium genavense infection. Aids. Mar 27 2015;29(6):745-6. doi:10.1097/qad.0000000000000568
6. Parisi A, Cafarotti A, Salvatore R, Pelliccia P, Breda L, Chiarelli F. Protein-losing enteropathy in an infant with rotavirus infection. Paediatr Int Child Health. 2018; 38(2): 154-157. doi:10.1080/20469047.2017.1295011
7. Rohani P, Karimi A, Tabatabaie SR, Khalili M, Sayyari A. Protein losing enteropathy and pneumatosis intestinalis in a child with COVID 19 infection. J Pediatr Surg Case Rep. 2021; 64: 101667. doi:10.1016/j.epsc.2020.101667
8. Boyum RD, Au Yeung KJ, Kaplan KJ, Lipton AJ, Rogers PL. Pediatric Gastrointestinal Sarcoidosis Presenting With Protein-losing Enteropathy. Journal of Pediatric Gastroenterology and Nutrition. 2007; 44(1): 152-156. doi:10.1097/01.mpg.0000235976.52249.ec
9. Iwanaga M, Zaitsu M, Ishii E, et al. Protein-losing gastroenteropathy and retinitis associated with cytomegalovirus infection in an immunocompetent infant: a case report. European Journal of Pediatrics. 2004/02/01 2004; 163(2): 81-84. doi:10.1007/s00431-003-1372-y
10. Itkin M, Piccoli DA, Nadolski G, et al. Protein-Losing Enteropathy in Patients With Congenital Heart Disease. Journal of the American College of Cardiology. 2017; 69(24): 2929-2937. doi:doi:10.1016/j.jacc.2017.04.023
11. van de Ven AA, Douma JW, Rademaker C, et al. Pleconaril-Resistant Chronic Parechovirus-Associated Enteropathy in Agammaglobulinaemia. Antiviral Therapy. 2011; 16(4): 611-614. doi:10.3851/imp1792
12. Hassan E, Baldridge MT. Norovirus encounters in the gut: multifaceted interactions and disease outcomes. Mucosal Immunology. 2019/11/01 2019; 12(6): 1259-1267. doi:10.1038/s41385-019-0199-4
13. Karbach U, Ewe K, Bodenstein H. Alpha 1-antitrypsin, a reliable endogenous marker for intestinal protein loss and its application in patients with Crohn's disease. Gut. 1983; 24(8): 718-723. doi:10.1136/gut.24.8.718

14. Akkelle BS, Tutar E, Sengul OK, Celikel CA, Ertem D. A Rare Complication of Giardiasis in Children: Protein-losing Enteropathy. The Pediatric Infectious Disease Journal. 2018; 37(12): e345-e347. doi:10.1097/inf.0000000000002025

15. Ferreira L, Amaral R, Gomes F, Cabral J. Protein-losing enteropathy caused by Yersinia enterocolitica colitis. Paediatrics and International Child Health. 2021/10/02 2021; 41(4): 291-294. doi:10.1080/20469047.2021.1890681

16. Iwasa T, Matsubayashi N. Protein-loosing enteropathy associated with rotavirus infection in an infant. World J Gastroenterol. 2008; 14(10): 1630-2. doi:10.3748/wjg.14.1630

17. Hoshina T, Kusuhara K, Saito M, et al. Cytomegalovirus-Associated Protein-Losing Enteropathy Resulting from Lymphangiectasia in an Immunocompetent Child. Japanese Journal of Infectious Diseases. 2009; 62(3): 236-238. doi:10.7883/yoken.JJID.2009.236

18. Russo T, Costa C, Crujo C, Lopes AI. Protein-losing gastropathy associated with cytomegalovirus infection in a child. BMJ Case Rep. 2012; 2012. doi:10.1136/bcr.01.2012.5679

19. Xi Y, Chen Z, Hao K, Liu X. Case Report: Protein-Losing Enteropathy in Association With Tuberculosis-Related Constrictive Pericarditis. Front Pediatr. 2022; 10: 875032. doi:10.3389/fped.2022.875032

20. Nakamura A, Fuchigami T, Inamo Y. Protein-losing enteropathy associated with Henoch-Schönlein purpura. Pediatr Rep. 2010; 2(2): e20. doi:10.4081/pr.2010.e20