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Protein-Losing Enteropathy in the Setting of Iron Deficiency Anemia: A Case Series

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Abstract: Protein-losing enteropathy (PLE) in the setting of severe iron deficiency anemia (IDA) and excessive cow milk intake is an uncommonly recognized phenomenon. Here, we describe a series of 7 toddlers who presented for evaluation of edema in the setting of excessive cow milk intake between November 2016 and January 2019. Laboratory studies in each patient were consistent with IDA and hypoalbuminemia with evidence of PLE. Diagnostic evaluation and treatment of each patient differed, although all were instructed to restrict cow milk and provided with oral iron supplementation. The edema had resolved, and the IDA had improved in all 7 patients by the time of their follow-up outpatient appointments. Iron deficiency and PLE should be considered in patients who present with anasarca.

What Is Known?

- Protein-losing enteropathy (PLE) has been observed in patients presenting with severe iron deficiency anemia (IDA) in the setting of cow milk intake.
- Iron deficiency is the most common nutritional deficiency in children in the United States.

What Is New?

- The approach to PLE in patients with IDA varies with respect to clinical recognition, diagnostic approach, and treatment.
- Symptoms of PLE typically resolve in response to restriction of cow milk and oral iron supplementation.

INTRODUCTION

Iron deficiency (ID) is the most common nutritional deficiency in children. It is estimated that 7%–9% of toddlers in the United States are iron deficient, and approximately 3% manifest iron deficiency anemia (IDA).[1] Consequences of IDA can include impaired neurocognitive development, visual and auditory processing, and exercise capacity.[2] Protein-losing enteropathy (PLE) is characterized by the loss of proteins through the gastrointestinal tract leading to hypoalbuminemia and hypoproteinemia. Case series of toddlers presenting with PLE in the setting of severe IDA and excessive cow milk intake have been reported. [3–6] However, most of these reports were compiled before the widespread fortification of infant formulas and cereal with iron in the 1940s. As such, many clinicians in practice today may be less aware of this association when considering likely etiologies of PLE and edema in young pediatric patients.

This report examines 7 cases of toddlers with edema in the context of severe IDA who presented to a tertiary care institution between November 2016 and January 2019. The current study is an expansion of a single case report we previously published on the subject in 2018.[7] The aim of this case series is to highlight the importance of considering IDA and PLE in toddlers presenting with anasarca and to describe the nonuniform workup and treatment of this diagnosis.

METHODS

This study was reviewed by an institutional review board and determined to be exempt. Seven patients treated by our institution between November 2016 and January 2019 were identified to have symptoms and laboratory features of PLE (namely hypoalbuminemia and elevated alpha-1 antitrypsin in stool) and IDA (defined as anemia for age with transferrin saturation <16%). A retrospective review of the electronic medical records was completed for these 7 patients to abstract their presenting symptoms, laboratory data, treatment, and follow-up. Descriptive statistics, including medians and ranges, were calculated.

RESULTS

The median age at presentation was 20 months (range 14–27 mo). The most common presenting symptoms included periorbital edema, abdominal distension, and pallor. Changes in stooling patterns were noted in 3 cases (2 with diarrhea, 1 with constipation). All patients initially presented to primary care clinics and were subsequently referred for emergency department evaluation. Four patients required admission. All patients were otherwise healthy with normal growth parameters (average weight for length 73rd percentile, range 53rd–99th percentile).

History revealed that all patients were receiving a considerable amount (≥24 ounces/d) of cow milk in their diet (median 36 ounces, range 24–72 oz/d). Additional dietary information (including exposure to other dairy products) was not available for analysis in this retrospective chart review. The diagnostic evaluation included laboratory workup (Fig. 1 and Table 1). Laboratory evaluation revealed IDA and hypoalbuminemia in each patient. Interestingly, the severity of anemia and hypoalbuminemia were not comparable in each of the patients. Management strategies included the elimination of cow's milk and the initiation of oral iron (median dose 6 mg/kg/day; range 3–6 mg/kg/d). Four unique patients also received parenteral interventions including IV iron (N = 1), packed red blood cell (N = 3), or IV albumin (N = 2). Two patients required multiple parenteral therapies. Endoscopy and colonoscopy were completed in 2 patients, and both had grossly and histologically normal results.

The median changes in hemoglobin and albumin pre- and post-treatment were +5.4 g/dL (range 2.9–8.7) and +1.8 g/dL (range

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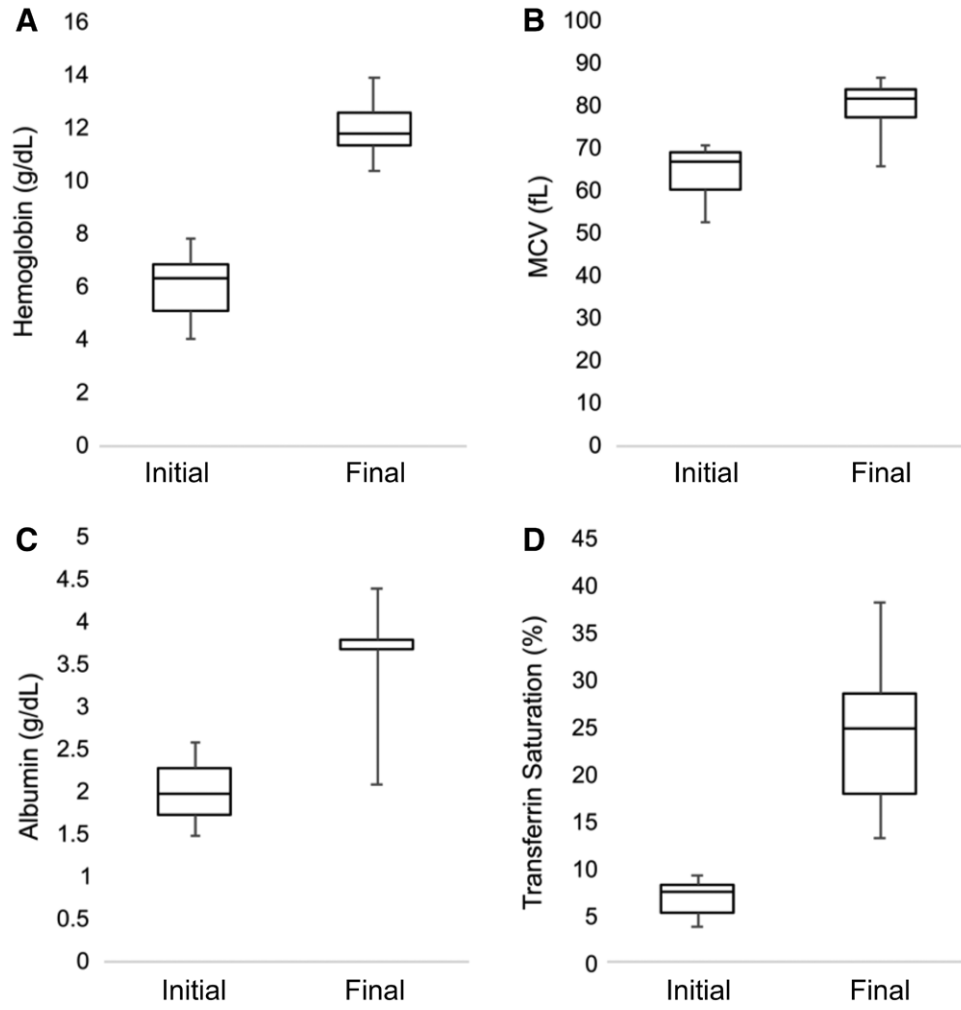

FIGURE 1. Hemoglobin, mean corpuscular volume (MCV), albumin, and transferrin saturation at the time of initial presentation and final follow-up.

0.2–2.8). After eliminating patients that received parenteral interventions, the median changes in hemoglobin and albumin in the remaining patients were +6.25 g/dL (range 2.9–7.1) and +1.6 g/dL (range 0.2–1.8), respectively.

Six of seven patients had hemoglobin levels >11 g/dL and normal serum ferritin levels at their follow-up visit about 3 months postdiagnosis. Five of seven patients had a transferrin saturation that was >15%, and edema had resolved in all patients.

DISCUSSION

This case series describes 7 otherwise healthy toddlers presenting with PLE in the setting of IDA. Milk-related IDA and PLE resulting from excessive cow milk have been previously described in the literature,[3–6] but this is a far less commonly reported clinical entity in contemporary practice. The data presented in this series highlights the nonuniform approach to workup and treatment in patients with PLE and IDA. There is no evidence or consensus-based approach to the assessment of these patients. This variation in care was apparent in the decisions about admission, treatment with parenteral or enteral iron supplementation, the transfusion of packed red cells or albumin, and the need for endoscopic and colonoscopic evaluation. Data presented here suggest that laboratory evaluation in children with PLE and IDA is helpful and should include a complete blood count, albumin, iron, ferritin, transferrin binding capacity, and stool alpha-1 antitrypsin. Fortunately, all patients had resolution of their edema and anasarca at the time of follow-up. However, one patient continued to be anemic and another patient continued to have laboratory evidence of ID. It is unclear from chart review why these lab abnormalities persisted in these 2 patients, although it is possible nonadherence with iron supplementation or cow milk restriction could be a cause.

The discordant approach to the diagnosis and management of these patients likely results from an incomplete understanding of the physiologic connection(s) between PLE and IDA. PLE is generally thought to result from a combination of either increased lymphatic pressure or ongoing inflammatory, erosive, or exudative disease of the gastrointestinal tract.[8] However, it is more likely that multiple overlapping mechanisms are operant in patients presenting with PLE and IDA. Iron deficiency may impair epithelial tight junction regulation, thereby increasing mucosal permeability and subsequent leakage of protein into the lumen of the gastrointestinal tract.[9] An alternative explanation is that excessive cow milk damages the intestinal epithelia directly, and this results in a loss of serum albumin as well as the iron that has been absorbed and sequestered in sloughed enterocytes.[10] It is unknown why some patients with IDA develop

TABLE 1. Clinical Characteristics at Presentation (a), Interventions (b), and Follow-up Data (c)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
(a) Clinical characteristics at presentation							
Age (mo)	16	20	27	20	20	15	14
Sex	M	F	F	F	M	F	F
Cow milk (oz/d)	72	24	32	30-50	24-30	32-40	Unk.
Presenting symptoms	A	PE	PE, P	A, AD	PE, D, AD, F	PE, F	P
Duration of symptoms	1 mo	Several months	1 mo	2 d	2 wks	3 wks	1 wk
Hemoglobin (g/dL)	6.5	4.3	6.4	7.2	7.9	5.9	2.5
MCV (fL)	57.8	67.2	67.5	63.5	71.1	71.3	52.8
Albumin (g/dL)	2.3	2.3	1.9	1.5	1.6	2	2.6
Transferrin saturation (%)	3.67	9.25	6.56	8.04	8.57	7.42	3.82
Fecal blood	–	–	+	+	+	+	+
Stool A1AT (mg/g)	>1.13	N/A	>1.13	>1.13	>1.13	>1.13	N/A
Proteinuria	–	N/A	–	N/A	–	–	N/A
(b) Interventions							
Admitted	No	Yes	No	Yes	Yes	No	Yes
EGD/colonoscopy	No	No	No	Normal	Normal	No	No
pRBC transfusion	No	10 mL/kg	No	No	15 mL/kg	No	15 mL/kg
Albumin infusion	No	No	No	Yes	Yes	No	No
Iron, route (dose; mg/kg/d)	Oral (6)	Oral (6)	Oral (6)	Oral (4)	Oral (6)	Oral (4.5)	IV (5), Oral (3)
(c) Follow-up laboratory values							
Hemoglobin (g/dL)	12.3	11.6	9.3	13.9	11.8	13	11.2
MCV (fL)	66.1	87.2	78.3	77.1	85.4	83.3	82.2
Albumin (g/dL)	N/A	N/A	2.1	3.7	4.4	3.8	3.7
Transferrin saturation (%)	24.78	28.18	14.81	20.82	38.22	13.18	29.01

A, anasarca; A1AT, alpha-1 antitrypsin; AD, abdominal distension; D, diarrhea; EGD, esophagogastroduodenoscopy; F, fatigue; MCV, mean corpuscular volume; P, pallor; PE, periorbital edema; pRBC, packed red blood cell.

PLE while many others do not, but the phenomenon is repeatedly reported in the literature with diagnostic evaluations failing to uncover alternative disorders.[3–7]

Two of the patients in this case series underwent upper endoscopy and colonoscopy, and both had normal gross and histologic findings. This suggests that any mucosal damage occurring in these patients (if present) must have been restricted to portions of the small bowel not accessible by standard upper endoscopy or colonoscopy. Previous reports of the endoscopic appearance of the small and large bowel mucosa of patients with PLE and IDA have similarly failed to identify gross or histologic abnormalities consistently.[3] As such, the role of upper endoscopic study and colonoscopic examination in the diagnosis of PLE-related IDA remains uncertain.

Cow milk intake above the recommended 16–24 oz/d was seen in all patients at the time of presentation.[11] Although strict elimination of cow milk was recommended to the families in this case series, data from a small randomized study suggests that cow milk restriction to 16 oz/d may be sufficient.[5] Similarly, all patients in this series were also prescribed a high dose (6 mg/kg/d) oral iron supplementation. Red blood cell or albumin infusions are likely only necessary in selected cases. We suggest that patients should have a follow-up visit about 4 weeks post-diagnosis to assess for the resolution of edema and compliance with iron supplementation and cow milk reduction.

The patients presented in this case series were collected over 27 months at a single tertiary care pediatric center. This small series likely underrepresents the incidence of this disorder, as it only included patients either admitted to a primary gastroenterology service or those receiving formal gastroenterology consultation. The prevalence of PLE as a presentation of IDA is not well characterized. To date, a single prospective study monitored for the development of PLE in patients with IDA and found that 29% of patients with IDA were also diagnosed with PLE.[5] Prospective data are needed to better characterize risk factors for developing PLE in children with cow milk associated IDA.

In conclusion, the association between high levels of cow milk intake, IDA, and PLE should be considered in toddlers presenting with a supporting dietary history and suggestive clinical features. The literature to date supports the correction of IDA, and possibly cow milk intake reduction, as treatment strategies for PLE in this population.

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