Unusual Presentation of Cow's Milk Protein Allergy

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Abstract: Cow's milk protein allergy (CMPA) is an abnormal immunologic response to bovine protein that can result in various gastrointestinal and cutaneous manifestations including diarrhea, failure to thrive, malabsorption, and even protein-losing enteropathy. We describe a case of a 7-month-old breastfed male who presented with severe atopic dermatitis, emesis, oily diarrhea, failure to thrive, electrolyte disturbance, and hemodynamic instability. Following stabilization, additional evaluation revealed concern for abetalipoproteinemia. Ultimately, the patient's symptoms resolved with introduction of an elemental formula and returned with reinitiation of cow's milk protein, confirming the diagnosis of severe CMPA. It is important for the general practitioner to be aware of the various presentations and have a high index of suspicion for CMPA as no symptom or diagnostic test is pathognomonic for diagnosis. Even though it can mimic other causes of malabsorption, a trial with extensively hydrolyzed or elemental formula should be attempted before undertaking invasive testing.

Key Words: abetalipoproteinemia, cow's milk protein allergy, failure to thrive

INTRODUCTION

The most common food allergen in infants and young children is cow's milk protein, which results from an abnormal immunologic response against bovine milk protein (1). Cow's milk protein allergy (CMPA) is a non-IgE mediated reaction to proteins found in cow's milk, which if persistent beyond infancy, is often termed food protein-induced enterocolitis syndrome. This differs from classic IgE-mediated food reactions, which occur within minutes to 2 hours of exposure and can include urticaria, angioedema, cough, wheezing, respiratory distress, severe abdominal pain, and vomiting (1). Symptoms of CMPA can include vomiting, diarrhea, rectal bleeding, and irritability. If symptoms are unrecognized and untreated, protein-losing enteropathy, hypoalbuminemia, and poor growth may ensue. Diagnosis of CMPA is made based on a high index of clinical suspicion (2). Due to the various presentations of CMPA, it can mimic several other disease processes. Here, we describe an unusual presentation of severe CMPA that was obscured by clinical and histological features of abetalipoproteinemia.

CASE PRESENTATION

A 7-month-old male born at 39 weeks gestation with a history of severe atopic dermatitis presented to the emergency department for evaluation of distress, lethargy, and poor growth. The infant was exclusively breastfed and reportedly had daily episodes of nonbloody, nonbilious emesis and 10–14 nonbloody, mucus-containing stools per day.

On physical examination, he was a cachectic, ill appearing infant with tachypnea and tachycardia. His weight was 4.16 kg. Mucus membranes were dry, and he was hypotonic with alopecia and severe atopic dermatitis.

His growth chart revealed that his weight had fallen from the 40th percentile at 2 months of age to below the 1st percentile (Fig. 1). Initial laboratory studies were significant for a serum sodium of 120 mmol/L with serum osmolality of 254 mOsm/kg along with a normocytic anemia, and thrombocytopenia (Table 1).

He was admitted to the pediatric intensive care unit where his electrolyte derangements were corrected and feeds were initiated with an elemental formula due to concern for possible CMPA. Within 48 hours, his emesis and diarrhea resolved.

Further workup revealed decreased fat-soluble vitamins, elevated qualitative fecal fat (Table 1), and a complete abdominal ultrasound, which revealed normal anatomic structure with moderate ascites (in the setting of a serum albumin of 2.0 g/dL).

Histopathologic examination of esophagogastroduodenoscopy and flexible sigmoidoscopy revealed mild inflammation in the gastric body and increased epithelial cytoplasmic lipid droplets with preserved villous architecture in the duodenum (Figs. 2 and 3). The features of low fat-soluble vitamins, elevated fecal fat, and abnormal small bowel biopsies raised suspicion for abetalipoproteinemia, especially in the context of a blood smear showing acanthocytes, low apolipoprotein (apo) B level, and a low serum cholesterol (Table 1).

He was started on a specialized low long chain triglyceride + high medium chain triglyceride formula containing cow's milk protein, which was not tolerated and resulted in emesis and development of an erythematous facial rash. He was switched back to an elemental formula with medium chain triglyceride supplementation with resolution of symptoms. The patient was discharged after 2.5 weeks with improvement in weight by an average of 45 grams per day.

His genetic testing was ultimately not consistent with a diagnosis of abetalipoproteinemia and over the following year, his fat-soluble vitamin levels improved and remained stable following discontinuation of oral supplementation. He demonstrated good weight gain (Fig. 1) on an elemental formula and nondairy containing solid foods with transition to an elemental toddler formula at 12 months of age.

DISCUSSION

Our patient's presentation of failure to thrive (FTT), oily stools, and laboratory abnormalities suggestive of fat malabsorption challenged us to consider a variety of differential diagnoses including

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The parents of the subject provided informed consent to publish the details of this case.

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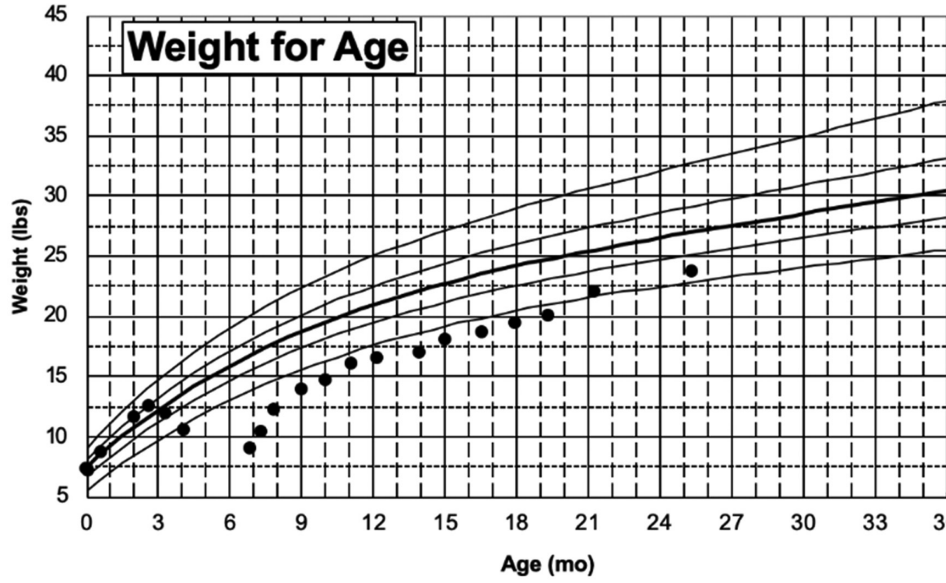

FIGURE 1. A picture of our patient's growth chart demonstrating failure to thrive. His symptoms started at 2 months of age with eczema, emesis, and diarrhea with oily stools. His weight declined until he was admitted to the hospital at 7 months of age. He demonstrated normal weight gain 1 year after discharge.

inflammatory states, protein-losing enteropathy, congenital diarrheal disorders, inborn errors of metabolism, immunodeficiency, pancreatic insufficiency, abetalipoproteinemia, chylomicron retention disease, and CMPA. His diagnosis of severe CMPA was ultimately confirmed with resolution of his symptoms with introduction of an elemental formula followed by recrudescence of symptoms upon reintroduction of cow's milk protein.

The differential diagnosis of FTT is quite diverse and broad. It can occur from a variety of both organic and nonorganic etiologies. This can include basic mechanisms of inadequate caloric intake, malabsorption, maldigestion secondary to diarrhea, or increased metabolic demand such as seen with congenital heart disease. Initial evaluation involves taking a detailed history, including feeding practices and formula preparation, identifying contributing factors and obtaining basic labs such as a complete blood count, comprehensive metabolic panel, magnesium, phosphorus, thyroid stimulating hormone, inflammatory markers, screens for inborn error of metabolism, and stool studies such as fecal elastase (3).

Abetalipoproteinemia is an autosomal recessive disorder in which a defect occurs in the formation of the microsomal triglyceride protein (MTP), which facilitates transfer of lipids onto apo B. Abnormal formation of MTP results in an absence of chylomicrons, low-density lipoproteins, and very-low-density lipoproteins leading to fat malabsorption, fat-soluble vitamin deficiency, and FTT (4). In addition to low apo B levels and evidence of fat malabsorption, the diagnosis requires confirmation by genetic testing. Ultimately, our patient's genetic testing did not reveal defects in the *MTP* gene indicating he did not have abetalipoproteinemia, which was later confirmed by his ability to maintain normal fat-soluble vitamin levels following supplement discontinuation. His extreme presentation was most likely a result of severe malabsorption secondary to CMPA since he gained weight and maintained normal fat-soluble vitamin levels while on the amino acid formula.

CMPA is estimated to have an incidence of 2% to 7.5% in infants less than 1 year of age, and it can occur in both breastfed and formula fed infants (5). The treatment of CMPA involves removal of all cow's milk protein from the child's diet. For breastfed infants, this requires the mother to eliminate cow's milk from her diet. For formula fed infants, this involves providing the infant with an alternative formula. North America Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommend infants <6 months of age be fed an extensively hydrolyzed or an amino acid-based (elemental) formula (6). A trial of soy-based formula is not recommended in this age group due to the 10 percent risk of cross-reactivity; however, may be trialed in infants older than 6 months of age due to the poor palatability of the other formula options (6,7). Half of children with CMPA have resolution by 12 months of age and 80%–90% have resolution within 5 years (1). Resolution of cow's milk protein-induced food protein-induced enterocolitis syndrome occurs at a median of 6.7 years in the United States (8). Children should be reevaluated every 6 months after 12 months of age to determine if the child is a candidate for reintroduction of cow's milk (6).

Our patient's clinical presentation and laboratory and histological findings demonstrated that CMPA can manifest as severe fat malabsorption, FTT, electrolyte abnormalities, and hemodynamic instability. This is due to the effect CMPA has on nutrient passage through the intestinal tract. Studies have shown evidence of jejunal mucosal damage resulting in rapid intestinal transit, which can lead to decreased nutrient and micronutrient absorption (9).

Even though CMPA can mimic other causes of malabsorption, it is important for pediatric medical care providers to be aware of such various presentations and have a high index of suspicion for CMPA as no specific symptom nor diagnostic test is pathognomonic for the diagnosis. In certain clinical scenarios, a trial with extensively hydrolyzed or elemental formula should be attempted with monitoring for symptom resolution. This approach can be beneficial to the patient prior to undertaking an extensive and invasive evaluation.

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S.C. conceptualized and designed the study, drafted the initial article, reviewed and revised the article, and attests to the established criteria for authorship by the International Committee of Medical Journal Editors (ICMJE). A.S. collected data, carried out the initial analyses, reviewed and revised the article, and attests to the established criteria for authorship by the ICMJE. H.G. prepared the

TABLE 1. Initial complete blood count panel and comprehensive metabolic panel obtained upon presentation to the emergency department as well as subsequent lab evaluation obtained throughout hospitalization.

Serum	Patient value	Reference range and units
WBC	17.2	6.0–17.5 thou/cu mm
RBC	3.63	3.10–4.50 × 10E6/uL
Hemoglobin	9.4 (L)	9.5–13.5 g/dL
Hematocrit	27.2 (L)	29.0%–41.0%
MCV	75	74.0–108.0 fl
MCH	26	25.0–35.0 pg
MCHC	34.7	31.0–37.0 g/dL
RDW	14.7 (H)	11.0%–14.0%
Platelet count	1156 (H)	150–450 thou/cu mm
MPV	5.9 (L)	6.0–10.0 fl
Sodium	120 (L)	136–145 mmol/L
Potassium	5.1	3.3–5.1 mmol/L
Chloride	98	98–107 mmol/L
CO_2	15 (L)	22–30 mmol/L
Urea nitrogen	10	6–21 mg/dL
Creatinine	<0.20	0.10–0.36 mg/dL
Glucose	100 (H)	65–99 mg/dL
Calcium	7.8 (L)	8.4–10.2 mg/dL
Total protein	3.8 (L)	6.4–8.3 g/dL
Albumin	2.0 (L)	3.5–5.2 g/dL
Calc total globulin	1.8	g/dL
Albumin/globulin ratio	1.1	(calc)
Total bilirubin	0.3	0.0–1.0 mg/dL
Alkaline phosphatase	102 (L)	116–450 IU/L
AST	36	0–37 IU/L
ALT	29	0–50 IU/L
Osmolality	254 (L)	275–295 mOsm/Kg
Amylase	<10 (L)	28–100 U/L
Cholesterol, total	67 (L)	115–169 mg/dL
Triglycerides (fasting)	83	30–124 mg/dL
HDL	35	23–92 mg/dL
LDL calculated	15	mg/dL
Apolipoprotein B	49 (L)	55–140 mg/dL
Apolipoprotein A1	106	94–178 mg/dL
Vitamin A	0.17 (L)	0.20–0.50 mg/L
Vitamin D	<7 (L)	20–120 ng/mL
Vitamin E	3.4	0.0–6.0 mg/L
Vitamin K	0.19 (L)	0.22–4.88 nmol/L
Zinc	49 (L)	60–120 µg/dL
Stool	**Patient value**	**Reference range and units**
Fecal occult blood	Positive	Negative
Fecal calprotectin	76 (H)	≤50 µg/g
Qualitative fecal fat	Increased	Normal
Helicobacter pylori antigen	Negative	Negative

AST = aspartate aminotransferase; ALT = alanine transaminase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC mean corpuscular hemoglobin concentration; MPV = mean platelet volume; RDW = red blood cell distribution width; RBC = red blood cell count; WBC = white blood cell count.

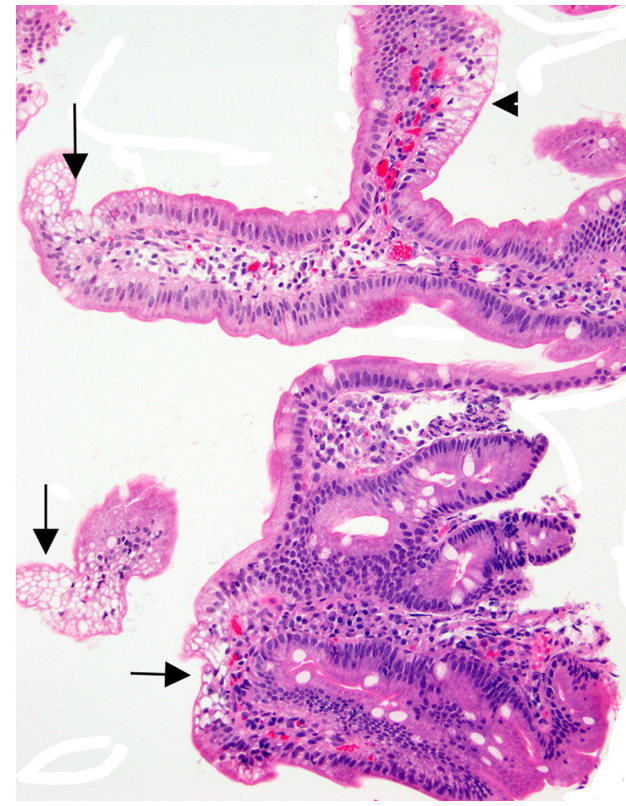

FIGURE 2. Duodenal mucosa with intact villous architecture and increased epithelial cytoplasmic lipid droplets (see arrows). Arrowhead corresponds to epithelium shown in Figure 3 at higher magnification (H&E staining, original magnification ×200). H&E = hematoxylin and eosin.

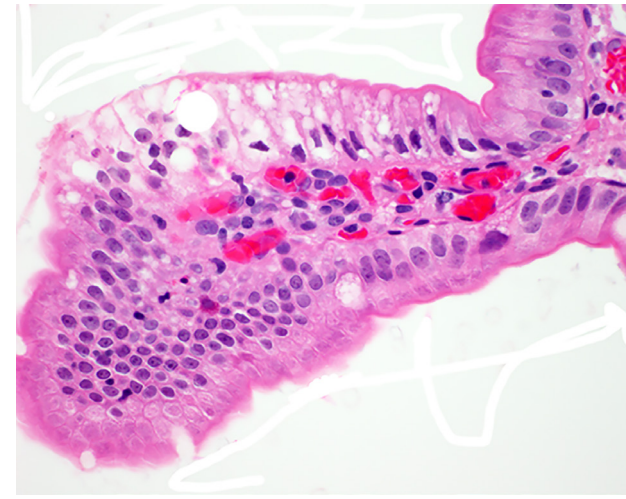

FIGURE 3. Compare normal duodenal epithelium on the lower aspect of the villus versus the abnormal epithelium with lipid droplets on the upper aspect. No increased intraepithelial lymphocytes are identified (H&E staining, original magnification ×600). H&E = hematoxylin and eosin.

esophagogastroduodenoscopy histology slides and figures, reviewed and revised the article, and attests to the established criteria for authorship by the ICMJE. G.B. and A.C. coordinated and supervised data

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