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Introduction

Cow's milk protein allergy (CMPA) is the third most common food allergy in pediatrics, following allergies to peanuts and tree nuts.^{1–3} The prevalence of CMPA is reported to be 2.2% to 2.8% at 1 year of age,^{4,5} and cow's milk protein (CMP) comprises 10% to 19% of food-induced anaphylaxis.^{1–3} IgE-mediated CMPA usually manifests with respiratory, cutaneous, and/or gastrointestinal symptoms, which appear immediately, whereas non-IgE-mediated clinical syndromes have a delayed presentation and include food protein–induced enterocolitis, eczema, eosinophilic esophagitis, CMP-induced gastroesophageal reflux disease, enteropathy, proctocolitis, colic, and constipation.⁶ Thrombocytopenia as a manifestation has been sparsely described in old literature from the early 1980s. In this case report, we present an infant with thrombocytopenia associated with CMPA.

Case Report

The index case was a 2-month-old male born at term (birth weight 2.3 kg, <fifth percentile) with no immediate complications who was transferred to our institution with a 1-month history of subjective fevers and diarrhea, which had been getting worse for the past 2 weeks. Before presentation, he had been having up to 15 loose stools per day described as yellow, foul smelling, and containing mucus but no visible blood. The patient's primary care pediatrician suspected CMPA and changed his formula from an intact protein-based formula to a soy-based formula, but the patient did not tolerate it well and started having increased spitting up and vomiting; so his mother switched the formula back to the intact protein cow's milk–based formula. He presented to an outside emergency room, where he was found to be lethargic, malnourished, and severely dehydrated. Initial labs revealed hyponatremia, hyperkalemia, hypoalbuminemia, anemia, leukocytosis with bandemia, and thrombocytopenia. Rehydration via the intraosseous route was initiated because of difficulty in securing an

intravenous (IV) access, and the patient was transferred to our institution.

The patient was admitted to the pediatric intensive care unit (PICU), and his vitals on arrival were as follows: temperature, 97.1°F; heart rate, 168/min; blood pressure, 116/58 mm Hg; respiratory rate, 35/min; oxygen saturation, 100% on room air; and weight on admission, 2.98 kg (<fifth percentile). Physical examination revealed severe (15%) dehydration with a sunken fontanelle, delayed capillary refill of 4 seconds, 1+ distal pulses, and poor skin turgor. Other than the decreased amount of subcutaneous fat, examination of the other systems did not reveal any significant abnormalities. Labs on admission to our PICU were as follows: sodium, 124 mmol/L; potassium, 6.5 mmol/L; chloride, 105 mmol/L; bicarbonate, 10 mmol/L; blood urea nitrogen (BUN), 21 mg/dL; creatinine, 0.3 mg/dL; glucose, 52 mg/dL; calcium, 8 mg/dL; total protein, 4.3 g/dL; albumin, 1.2 g/dL; total bilirubin, 0.7 mg/dL; aspartate aminotransferase (AST), 18 U/L; ALT, 10 U/L; alkaline phosphatase, 104 U/L; hemoglobin, 5.2 g/dL; hematocrit, 15.2%; mean corpuscular volume (MCV), 76 fL; reticulocyte count, 2.67%; white blood cell count (WBC), 23 580/mm³ with 56% segments, 8% bands, 22% lymphocytes, 12% monocytes, and 2% eosinophils; and platelet count 191 000/mm³. After establishing access via the right external jugular vein, appropriate IV fluid therapy for rehydration and correction of hyponatremia was initiated. The patient was kept NPO (nothing by mouth), and IV antibiotics were started for presumed sepsis. His stools tested positive for occult blood. Hyponatremia and dehydration were corrected over 48 hours, and he received 2 packed red blood cells and three 25% albumin

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transfusions over this 48-hour period. Significantly, his platelet counts decreased and were $62\,000/\text{mm}^3$ on day 2 of admission. Moreover, he continued to have multiple loose stools per day despite not receiving enteral nutrition. Echocardiogram, abdominal ultrasound, and barium swallow with a small bowel follow through did not reveal any abnormalities. He was transferred to the pediatric floor on day 3 where feeds were initiated with an amino acid-based formula (AAF; Neocate), 20 kcal/oz. He remained afebrile and cultures remained negative, and therefore, his antibiotics were discontinued. He continued to have 8 to 10 occasionally heme-occult positive stools per day over the next few days, and an attempt to increase the caloric content of the feeds to 22 kcal/oz failed because of increase in the number of bowel movements. His amino acid levels were within normal range, and the newborn screen was found to be normal. He continued to have thrombocytopenia and his platelet count improved slightly from $66\,000/\text{mm}^3$ to $76\,000/\text{mm}^3$ but dropped again to $60\,000/\text{mm}^3$ the next day. The hemoglobin and hematocrit were 7.7 g/dL and 22.3% and were stable. A coagulation profile was ordered, and it revealed the following: prothrombin time (PT) = 14.2 s; activated partial thromboplastin time (APTT) = 35.4 s; international normalized ratio (INR) = 1.4; D-dimer < 0.17 mg/L; and fibrin = 92 mg/dL. Some decrease in frequency and increase in consistency of stools was seen, and by day 5, the patient was having 6 to 8 stools/d, still occasionally positive for occult blood. With persistence of occult blood–positive diarrhea and poor tolerance to increase in feedings, esophagogastroduodenoscopy and flexible sigmoidoscopy were done and were visually normal. Biopsies revealed mild chronic nonactive gastritis, focal acute inflammation in the small bowel, and minimal architectural disarray in the rectosigmoid region on microscopy with no significant eosinophilic infiltrates. After completion of endoscopic evaluation, his diarrhea continued to improve, and the stool frequency decreased to 3 to 4 per day of occult blood–negative stools. After 2 days, his hematology results were as follows: hemoglobin, 7.2 g/dL; hematocrit, 22.7%; reticulocyte count, 1.69%; WBC, $14\,110/\text{mm}^3$ with 27% segments, 1% bands, 54% lymphocytes, 15% monocytes, 3% eosinophils, and an improved platelet count of $234\,000/\text{mm}^3$; PT, 11.8 s; APTT, 32.4 s; INR, 1.1; and fibrin, 224 mg/dL. The patient was discharged on day 10, and his discharge weight was 3.52 kg (+540 g).

Discussion

This infant's presentation with feeding intolerance, poor weight gain, and diarrhea while being on a cow's milk-based formula is relatively common; 25% of infants <6 months of age with CMPA can also have soy protein

allergy, as was seen in this case with worsening of symptoms after introduction of a soy milk-based formula.⁷ The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the Australian expert panel recommend replacing CMP-based formulas by extensively hydrolyzed formulas (eHFs) in infants <6 months of age and consider transition to soy milk-based formulas only in infants older than 6 months because of a higher rate of concurrent soy allergy observed in the younger age group (25% vs 5%).⁷⁻⁹ The AAP, however, recommends the use of soy milk-based formulas before the use of eHF in the treatment of CMPA irrespective of age, with consideration of eHF.¹⁰ It is found that 10% of infants do not tolerate eHF and require transition to an AAF.⁸ In our case, after ruling out sepsis, we changed the infant's formula directly to an AAF based on his weight, clinical condition, and severity of symptoms. Most of his electrolyte abnormalities were attributed to dehydration and malnutrition, and his anemia was thought to be a mixture of blood loss, poor nutritional status, and physiological anemia. Although controlled food challenge has been long considered the gold standard for diagnosis, most clinicians use resolution of symptoms after complete avoidance as evidence of CMPA because of substantial risks associated with the former.¹¹ Laboratory investigations and endoscopies with biopsies are not diagnostic but often support a diagnosis based on clinical grounds, as was seen in this 2-month-old. Resolution of symptoms was seen after a week of complete avoidance of CMP. Of note, our patient was never administered ranitidine, a H₂ receptor blocker, which has been shown to cause varying amounts of thrombocytopenias.^{12,13}

The medical literature has only a handful of case reports associating thrombocytopenia with CMPA, most of which date back to the early 1980s. As with our patient, the cases described were found to be thrombocytopenic, and the platelet counts normalized after complete avoidance of CMP. In some cases, the thrombocytopenia reappeared on reintroduction of CMP on more than 1 occasion. Whitfield and Barr¹⁴ describe a newborn with the syndrome of thrombocytopenia and absent radius who exhibited aggravation of the thrombocytopenia, and diarrhea and vomiting (leading to dehydration) on reintroduction of CMP on 3 different occasions and resolution on avoidance. Similarly, Similä et al¹⁵ present the case of an 11-week-old with Down's syndrome with a typical picture of protein-losing enteropathy complicated by thrombocytopenia whose platelet counts normalized within 2 weeks after withdrawal of CMP from the diet. Both direct and indirect mechanisms may be implicated in thrombocytopenia associated with CMPA, wherein the direct destruction of platelets in

CMPA would likely be non-IgE mediated and could involve both humoral and/or cell-mediated mechanisms. Indirect mechanisms leading to thrombocytopenia may be seen in patients suffering from enteropathy caused by CMPA because excessive loss of inhibitors of coagulation secondary to protein losses may lead to a hypercoagulable state, which in turn leads to the consumption of thrombocytes, as was evident in our patient with thrombocytopenia and a deranged coagulation profile.

Conclusion

In this case report, we discussed CMPA complicated by a low platelet count, putting the patient at a risk of bleeding in addition to the gastrointestinal manifestations. We encourage reporting of thrombocytopenia seen in relation to not only CMPA but also to other food-related allergies because this may lead to further observations and research, which would allow for a more detailed explanation of the underlying mechanisms. We recommend obtaining complete blood counts in patients with suspected CMPA on a regular basis. Finally, food-based allergies should be excluded in all cases of idiopathic thrombocytopenia.

Declaration of Conflicting Interests

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