



Case Report

Palpebral Edema and Microcytic Anemia in a 2 Year-old Female with an Excessive intake of Cow's Milk

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Introduction

In young children prolonged and excessive Cow's Milk (CM) ingestion has the potential to cause a number of medical concerns [1]. We present here a child with a clinical presentation that suggested a milk-induced process [1]. We outline the evolution of the correct diagnosis with the potential milk-induced possibilities of causation.

Case Report

A 22-month-old girl of Vietnamese descent with a history of food allergies (shrimp) and mild atopic dermatitis presented to the emergency department with a 2-week history of periorbital edema, and one day of fever. A review of systems revealed a dark stool 4-5 days prior to admission. On physical exam she has conjunctival pallor, periorbital edema, tachycardia, a 2/6 systolic heart murmur and there was pitting edema in the lower extremities. Initial laboratory test revealed: Hematology: severe microcytic anemia (Hb 5.1 MCV 57.5), thrombocytosis (Platelets 591,000), eosinophilia (10%), low iron levels, low iron saturation, low total iron binding capacity. Chemistry revealed hyponatremia (131) and hypoalbuminemia (2.1). Urinalysis: negative for proteinuria. Respiratory viral panel was positive for coronavirus. Imaging: an abdominal ultrasound showed borderline splenomegaly, an echocardiogram showed normal cardiac function and no structural abnormalities. She was admitted, received a packed red cell transfusion, and the hemoglobin and hematocrit increased appropriately.

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An evaluation by clinical nutrition concluded that the patient had an inadequate protein intake due to a diet that consisted mainly of rice soup and whole Cow's Milk (CM). Intact cow's milk protein formula was re-started 240 ml 2-3 times per day. Hematology was consulted, and their opinion was her anemia was likely due to nutritional iron deficiency and a component of anemia of chronic disease. She was therefore started on oral ferrous sulfate. A fecal occult blood test was positive. At that point it was thought that the excessive consumption of CM was the etiology of her anemia, and gastrointestinal protein loss, she was referred to the Gastroenterology Clinic (GI) as an outpatient.

In GI clinic, she had lost 400 g in approximately a month. Her physical exam was unchanged. Expanded laboratory testing showed improved anemia, increased iron and iron saturation, persistent eosinophilia, persistent hypoalbuminemia. Folate, vitamin B12, vitamin D3, liver enzymes, INR, all were normal. Stool analysis revealed fecal occult blood, lactoferrin positive, Alpha-1 anti-trypsin in the stool was 490. Stool culture was negative, including giardia duodenalis and cryptosporidium parvum.

The decision was made to evaluate endoscopically with an EGD and flexible sigmoidoscopy. On the EGD there was visualized furrowing in the esophagus and patchy erythema in the duodenum. Microscopic exam revealed esophageal basal cell hyperplasia and spongiosis, with 70 eosinophils/High Power Field (HPF) in the proximal esophagus and 45 eosinophils/HPF in the distal esophagus. The gastric antrum showed > 100 eosinophils/HPF. The duodenum showed mild focal villous blunting, with >100 eosinophils/HPF. The Recto-sigmoid colon showed no macroscopic or microscopic abnormalities.

She referred to the Allergy-Immunology clinic. On physical exam she was noted to have atopic dermatitis and mild facial and peripheral edema. She was instructed to avoid dairy (the CM allergy skin test was negative), change the intact cow milk protein formula supplement to soy (allergy test negative), start omeprazole 1 mg/kg/day and swallow budesonide 500 mcg twice daily. She had subsequent emesis with the soy milk and was transitioned to a completely hydrolyzed formula. A repeat endoscopy 8 weeks later showed complete resolution of the tissue eosinophilia.

She is followed in Allergy-Immunology Clinic. Her atopic dermatitis is minimal, and she avoids milk and soy but ingests pea milk. Her ImmunoCap IgE tests are positive to shrimp, egg, peanut and tree nuts, and she avoids these foods.

Discussion

The intent of this case report is to emphasize the multiple possible medical conditions that may result from the excessive intake of milk. In the reported case, the presence of significant anemia, with hypoalbuminemia and eosinophilia were the critical elements that hallmarked the eventual diagnosis of eosinophilic gastroenteritis. Each of the critical components of the history, did however, suggest other potential diagnoses.

The initial concern was the severe iron deficiency anemia that is common in toddlers who consume large amounts of cow's-milk. In fact, is the most common cause during the second year of life [2]. CM impacts iron storages at all levels and it is an iron poor food. Its high content of casein, calcium, phosphorus, and a low Vitamin-C decreases the bioavailability of the iron it contains; furthermore CM has been associated with chronic GI losses [3]. The non-improvement at follow-up necessitated further evaluation.

The explanation of the hypoalbuminemia was initially less clear. Protein losing enteropathy associated with (or caused by) cow's milk ingestion has also been described although is rare, and its mechanism is not well understood [4,5]. It is hypothesized that the anemia and ferropenia negatively impact tissue metabolism and contribute to mucosal barrier dysfunction [4]. The original anemia was likely caused by excessive cow's milk ingestion, and the uncommon, but reported, milk associated protein losing enteropathy was advanced as a further complication of the excessive cow's milk ingestion [6].

The underlying atopic dermatitis with food allergy (shrimp) was originally considered a separate disease process, resulting in eosinophilia. However, the continued clinic picture at the GI clinic visit necessitated the esophagogastroduodenoscopy and colonoscopy with biopsies. The findings were compatible with pan-eosinophilic enteritis with associated protein losing enteropathy. First described in 1937, eosinophilic gastroenteritis (EGID) refers to a histologic infiltration of eosinophils in the GI tract at any point from the proximal esophagus to the anus [7,8]. A rare condition, it can present at any age; the peak incidence is seen in pediatric patients < 5yr, and a publication of a small number of pediatric "allergic gastroenteropathy" cases (EGID) is of historical interest [7-9]. The pathophysiology of eosinophilic gastroenteritis is not completely understood. Both IGE-mediated inflammation and non-IgE-mediated phenomena play a role [7,8].

There are 3 categories of EG as described by Klein in 1970, mucosal, muscular, and serosal form. Symptoms vary according to the affected layer [10]. The most common symptoms are abdominal pain, bloating, weight loss, dysphagia and vomiting [7,8]. Uncommon presentations include acute abdominal pain that mimics appendicitis. Colonic obstruction, abdominal distention, eosinophilic ascites and bowel perforation can occur, based on the bowel wall layer involved. A Medscape review of eosinophilic enteritis is available (<https://www.medscape.com/viewarticle/772972>).

Protein losing enteropathy and failure to thrive with pediatric EGID are typically seen in patient who have severe mucosal involvement [7,8]. A Medscape review of pediatric protein losing enteropathy in 2018 did mention EGID as a possibility. (<https://emedicine.medscape.com/article/931647-overview>). It is known that intestinal mast cells are significantly increased in the intestine in EGID, possibly causing increased intestinal permeability and protein loss [7,8].

The diagnostic workup for exaggerated gastrointestinal mucosal eosinophilia is directed at identifying all potential causes of tissue eosinophilic related conditions including, parasitic infestations, myeloproliferative dysplasia, congenital immune-deficiencies, HIV infection and systemic mastocytes and EGID's [7,8].

There is a lack of strong evidence regarding the best treatment for pediatric pan-EGID. EGID is considered an Type 2 (T_{H2}) immune disease, but routine IgE allergy testing results have been less useful,

and empiric elimination of allergy-associated foods (milk, wheat, eggs, peanut and soy) is the most used strategy with variable results in terms of symptom relief [7,8]. Corticosteroids have been used in adults with success [11]. Topical steroids are used to minimize the side effects profile and have been proven effective [12-14]. In the reported case the avoidance of cow's milk and swallowed corticosteroids (Budesonide) was successful, with resolution of anemia, hypoalbuminemia, and the gastrointestinal eosinophilia. The therapy options for EGID are reviewed in a recent Medscape report (<https://www.medscape.com/viewarticle/772972>). The natural history of EGID and pan-EGID in children is not known. Long-term surveillance is necessary.

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