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Severe Protein Loss in a 6-month-old Exclusively Breastfed Infant with Atopic Dermatitis

Mario Mašić[1], Iva Hojsak[1,2,3], Tena Niseteo[1], Nives Pustišek[4], Oleg Jadrešin[1], Irena Ivković-Jureković[1,3,5], Marta Navratil[3,5]

[1]Referral Centre for Pediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, Zagreb, Croatia; [2]University of Zagreb, School of Medicine, Zagreb, Croatia; [3]University of J.J. Strossmayer, School of Medicine, Osijek, Croatia; [4]Department of Dermatology, Children's Hospital Zagreb, Zagreb, Croatia; [5]Department of Pulmonology, Allergology, Immunology and Rheumatology, Children's Hospital Zagreb, Zagreb, Croatia;

Corresponding author:
Mario Mašić, MD
Referral Centre for Pediatric Gastroenterology and Nutrition
Children's Hospital Zagreb
Zagreb, Croatia
mmasic2@gmail.com

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ABSTRACT Protein loss is often the result of kidney or intestinal disease (protein-losing enteropathy) and can cause a number of serious, potentially life-threatening complications such as hypotension, thrombocytosis, electrolyte imbalance, and cerebellar ischemia. Recent research suggests an association between extremely severe atopic dermatitis (AD) and allergic enteropathy. An exclusively breastfed 6-month-old infant was admitted to our institution due to failure to thrive, electrolyte imbalance, and severe AD (SCORing Atopic Dermatitis; SCORAD 40). On admission, the infant was in poor general condition, dehydrated, malnourished (bodyweight 4870 g, -3.98 z-score), with exudative erythematous morphs scattered throughout the body. Initial laboratory results showed microcytic hypochromic anemia, hypoalbuminemia, hypogammaglobinemia, thrombocytosis, hyponatremia, high values of total immunoglobulin E (IgE), and eosinophilia. Polysensitization to a number of nutritional and inhalation allergens was demonstrated, and an exclusive amino acid-based formula has been introduced into the diet. During the hospital course, the patient developed superficial thrombophlebitis and methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. Eosinophilia was found in a small intestine biopsy sample. Due to severe hypogammaglobulinemia, skin infections, and bacteremia, the differential diagnosis included primary immune deficiency (STAT3 deficiency, DOCK8 deficiency, PGM3 deficiency, IPEX), but all available immunological tests were unremarkable. Exclusive amino acid-based formula diet was continued in the infant, with topical corticosteroids under wet-dressing therapy and intravenous immunoglobulin replacement therapy. With the gradual improvement of the general condition, the introduction of solid foods was started according to the findings of allergy testing. At 17 months of age, the patient gained weight and his skin status has been improving, although frequent use of topical corticosteroids was necessary. There were no infections, no anemia or thrombocytosis, and albumin and immunoglobulin supplementation were no longer required. The main mechanism of protein loss in infants with extremely severe atopic dermatitis is probably due to damaged skin, and partially due to the eosinophilic inflammation of the small intestine. Immunoglobulin loss, potentiated by physiological or transient hypogammaglobulinemia in infants, poses a very high risk for severe, potentially life-threatening infections.

KEY WORDS: atopic dermatitis, corticosteroids, eosinophilia, inflammation, hypersensitivity

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INTRODUCTION

Protein loss is often the result of kidney and/or intestinal disease (protein losing enteropathy) and can be the cause of serious, potentially life-threatening complications such as hypotension, thrombocytosis, electrolyte imbalance, and cerebellar ischemia. Recent research suggests an association between extremely severe atopic dermatitis (AD) and allergic enteropathy.

CASE PRESENTATION

An exclusively breastfed 6-month-old infant was admitted to the Department of Gastroenterology of our tertiary care hospital due to failure to thrive, edema, electrolyte imbalance, and severe atopic dermatitis (AD) (SCORing Atopic Dermatitis; SCORAD 40). He was the first child of non-consanguineous parents; born full term, birth weight 3600 grams (0.51 z-score). His father had asthma and Crohn's disease. The infant developed facial eczema at two months of age, which gradually spread diffusely to the whole body. Aiming to treat AD, the mother excluded cow's milk protein, egg, and gluten from her diet during a period of 4 weeks, but with no effect. Furthermore, the mother refused to use the topical corticosteroids and applied herbal creams on severely damaged skin lesions. On admission, the infant was in poor general condition, dehydrated, malnourished (body weight 4870 g, -3.98 z-score; body length 63 cm, -1.66 z-score), with exudative erythematous morphs scattered diffusely throughout the whole body. Initial laboratory results showed microcytic hypochromic anemia (Hb 110 g/L), hypoalbuminemia (IgA 0.2 g/L, IgM 0.34 g/L, IgG 1.02 g/L), hypogammaglobulinemia (IgG 1.02 g/L), thrombocytosis (1.600×10e9/L), hyponatremia (125 mmol/L), marked hyperkalemia (6.1 mmol/L), high values of total immunoglobulin E (IgE) (IgE – 2405 kU/L, normal <15),, and eosinophilia. There was no proteinuria. Upon arrival, parenteral rehydration was started with the supplementation of electrolytes, albumins, and immunoglobulins. Due to the severe clinical course and very anomalous values of the measured laboratory parameters, the infant underwent extensive diagnostic workup that included allergy (specific immunoglobulin E antibodies to egg white, milk, fish, soya bean, gluten, and walnut), and immunological tests, cardiological examination, cystic fibrosis and pancreatic insufficiency work-up, and hematological and dermatological examination. Cystic fibrosis (chloride in sweat <30 mEq/L) and pancreatic insufficiency (fecal elastasis 500 ug/g; normal > 200 ug/g) were excluded. Polysensitization to multiple nutritive and inhalation allergens was demonstrated, and an amino acid-based formula was introduced into the diet alongside with breastfeeding. The course of hospitalization was complicated with superficial thrombophlebitis and methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia treated with anti-aggregation therapy and vancomycin, which was further replaced by teicoplanin due to severe "red man" syndrome. The patient received a concentrated erythrocyte transfusion due to worsening of anemia. According to the initial presentation, clinical course, polysensitization to numerous allergens, unclear primary cause of protein loss (due to protein losing enteropathy or by skin damage due to severe AD), and a burdened family history (IBD), esophagogastroduodenoscopy and ileocolonoscopy were performed. In the small intestine biopsy sample, eosinophilia (>30 eosinophils per HPF) was found, without villous atrophy, granuloma, or cryptal abscess formation. Levels of calprotectin in the stool as a marker of intestinal inflammation were normal (<20 ug/g). We were not able to perform fecal alpha-1 antitrypsin clearance test or 99mTc-human serum albumin scintigraphy, as it was not technically available. Due to severe hypogammaglobulinemia, persistent skin infections, and MRSA bacteremia combined with high overall IgE and eosinophilia, differential diagnosis in our patient included a primary immunodeficiency disorder (STAT3 deficiency, DOCK8 deficiency, PGM3 deficiency, IPEX syndrome). All available immunological tests, immunophenotyping of peripheral blood lymphocytes, lymphocyte function, respiratory burst, bone marrow morphology, and thymus ultrasound were normal.

HOSPITAL COURSE

An exclusive amino acid-based formula diet was continued in the infant, with topical corticosteroids under wet-dressing therapy and intravenous immunoglobulin replacement therapy every 4 weeks. With the gradual improvement of the general condition and regression of the skin symptoms, introduction of solid foods was started according to the findings of the allergy testing. At 17 months of age, the patient gained weight (body weight 12.5 kg, 0.61 z-score), dermatological skin status was improved, but frequent use of topical corticosteroid preparations was still required. There were no infections, anemia or thrombocytosis, and albumin and immunoglobulin supplementation were no longer required.

FINAL DIAGNOSIS

Severe protein loss in severe atopic dermatitis (SPLAD), multiple nutritive allergies.

DISCUSSION

We presented a case of severe protein loss in infant with extremely severe atopic dermatitis, which was probably due to damaged skin and partially due to eosinophilic inflammation of the small intestine. AD is a chronic inflammatory skin disease common in children, which affects 5-20% children worldwide (1). Generally, it is accepted that AD is not a life-threatening disease, but in children it can be accompanied with serious, life-threatening conditions such as hypoproteinemia, hyponatremia, thrombocytosis, hypogammaglobulinemia, serious infections, and growth retardation (2-4). Protein loss in children mostly occurs due to renal or/and intestinal disease (protein-losing enteropathy) and can cause a number of potentially life-threatening complications such as hypotension, thrombocytosis, electrolyte imbalance, cerebellar ischemia, and in extreme cases death. Recent studies suggest that patients with AD associated with hypoproteinemia have high SCORAD scores, high levels of total IgE, polysensitization to various nutritive allergens, and early sensitization to *Dermatophagoides pteronyssinus* (5,6). Hypoproteinemia in these patients was likely caused by protein leakage through the damaged skin and intestine, poor food intake, inappropriate skin care, or because of fear of applying topical corticosteroids (steroid phobia), the latter being recognized as a global phenomenon that exacerbates AD (7). A decline in corticosteroid use also occurred in our patient, whose parents were initially reluctant to use corticosteroids, but the problem resolved with a multidisciplinary approach that included a great deal of patience, education, and persistence. In our patient, the symptoms first appeared at the age of two months, but were under recognized and neglected, as the eczema was disappearing and then reoccurring in more severe forms until the growth retardation (weight loss) was noted at the age of 5 months. The patient was admitted in poor general condition, and his clinical state improved through careful parenteral fluid, electrolyte, albumin, and immunoglobulin supplementation during three consecutive days. After stabilization, our first differential diagnosis was food protein-induced enteropathy syndrome (FPIES) and severe AD, but it was not clear whether the patient was losing proteins throughout the intestine or throughout the skin. We were not able to perform fecal alpha-1 antitrypsin (FAAT) clearance test or 99mTc-human serum albumin scintigraphy. However, according to studies, FAAT concentrations in children with and without AD were not significantly different, although it should be noted that patients in the study were 2-10 years of age, and not infants (8). In addition, as protein leakage through the intestine was believed to be a cause of hypoproteinemia, as some of the patients presented digestive symptoms, a study that compared fecal and skin lesion exudates confirmed that protein loss probably occurs throughout the damaged skin (6,9-11). The small bowel biopsy in our patient did not indicate villous atrophy; however, it confirmed eosinophilia, and fecal calprotectin levels, an inflammatory marker in the bowel, were normal (<20 ug/g in repeated samples). Coeliac disease was excluded as the coeliac-specific serology (anti-tTG antibodies) were negative (total IgA of 0.2 is considered enough to interpret the anti-tTG antibodies) and small intestine biopsy did not indicate villous atrophy or lymphocyte infiltration. Although, there could be possible limitations to excluding coeliac disease, as the child was already on exclusion diet from gluten for 3-4 weeks at that time. During follow-up, gluten was introduced into the diet without deterioration of skin status or the appearance of gastrointestinal or others symptoms, so coeliac disease is not probable. If the symptoms reoccur, a control endoscopy will be performed. Considering the evidence of eosinophilia in small bowel biopsy samples, polysensitization to multiple nutritive allergens, and a good clinical response after the introduction of amino acid-based formula, we still could not exclude the possibility of partial protein leakage throughout the intestine. The mechanism of protein loss in eosinophilic inflammation of the gut is still not clear. The protein loss could be the result of increased capillary leakage due to inflammation (12). In our patients there was no aphthous lesions in the gut, so protein loss could be the result of increased capillary leakage. The hospital course was further complicated by a methicillin-resistant strain of *Staphylococcus aureus* bacteremia. The role of damage to the skin barrier produced by *S. aureus* superantigens and the protein leakage worsening through the inflamed and damaged skin was previously described. Positive skin swab results for *S. aureus* superantigens in patients range from 66-100%, and the role of *S. aureus* superantigens in severe AD associated with hypoproteinemia requires further research (2,6,9). Given the age of the patient, our first therapeutic choice were topical glucocorticoids under occlusion (wet-dressings) with basic therapeutic agents (oily ointment bases), to which he responded well. Topical corticosteroids, given their potency, should be used according to severity, location of the lesions, and patient's age, taking into consideration that infants are more susceptible to undesirable effects (12). As the clinical status of our patient gradually improved, solid foods were introduced into the diet according to the results of allergy tests (specific IgE and skin prick

testing), along with an amino acid-based formula under a clinical nutritionist's supervision. In further follow-up, the patient gained body weight, with improvement in skin status, but still with frequent topical corticosteroid use. There were no complications regarding the skin and no systemic infections, no anemia or thrombocytosis, and no further immunoglobulin supplementations.

CONCLUSION

With the improvement of skin barrier, and with intensive supportive measures, while excluding other potential protein losing mechanisms and clinical entities, we showed that protein loss in this patient with extremely severe atopic dermatitis is probably due to severely damaged skin, and partially to the eosinophilic inflammation of the small intestine. Furthermore, immunoglobulin loss, potentiated by physiological or transient hypogammaglobulinemia in infants, poses a remarkably high risk for severe, potentially life-threatening infections. Further studies are still needed to investigate gastrointestinal protein loss in infants with severe atopic dermatitis and multiple nutritive allergies.

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