
Case report

Cow's milk allergy in a patient with hyper-IgE syndrome

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Background: Both hyper-IgE syndrome and food allergies can result in the early onset of skin rash, eosinophilia, and markedly elevated serum IgE. Occasionally, it can be difficult to distinguish the 2 disorders. Most patients with hyper-IgE syndrome do not have food allergy.

Objective: To describe a child with cow's milk allergy associated with hyper-IgE syndrome manifesting as failure to thrive (FTT).

Methods: Epicutaneous skin prick test to cow's milk, CAP radioallergosorbent test, atopy patch tests, and double-blind, placebo-controlled milk challenge (DBPCMC) were performed.

Results: During initial presentation at 3 weeks of age, the circulating eosinophil count increased from 13,800/mm³ to 44,254/mm³ within 2 weeks while taking cephalexin. Despite treatment, he had worsening rash and FTT at 10 weeks of age with an IgE level of 8,454 U/mL. After changing from an infant milk formula with whey protein to an amino acid-based formula in combination with oral antibiotic treatment, his rash and growth velocity improved markedly within 2 months. IgE decreased to 2,747 U/mL. He remained clinically well for 12 months. He subsequently developed additional food and inhalant allergies with an increase in IgE to 12,150 U/mL. Cow's milk allergy was confirmed by epicutaneous skin prick test, atopy patch test, and DBPCMC.

Conclusions: Traditional prophylactic antistaphylococcal antibiotics, in combination with Neocate formula, were effective in treating the early skin manifestations of hyper-IgE syndrome and FTT in this infant. Cow's milk protein allergy should be considered in patients with hyper-IgE syndrome and FTT.

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INTRODUCTION

Distinguishing between food allergy and hyper-IgE in infants with elevated IgE levels is often difficult. Both diseases may present with delayed growth or failure to thrive (FTT).^{1–3} Hyper-IgE syndrome often presents in the neonatal period.^{1,2,4} In this case report, we describe an infant presenting with recalcitrant dermatitis, who continued to have worsening skin lesions despite intermittent oral antibiotics. After the diagnosis of cow's milk allergy was made, the infant's feeding was changed to an amino acid-based formula, with marked improvement. The incidence of cow's milk allergy in infants with hyper-IgE syndrome is unknown. We report the case of an infant with hyper-IgE syndrome who benefited from diagnosis of cow's milk allergy and treatment with an elemental formula.

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METHODS

Case Subject

The patient was recruited for a case report based on retrospective medical record review from an allergy clinic. This case report was approved by the University of Tennessee Health Science Center Institutional Review Board. Informed consent was obtained from the patient's parents.

Epicutaneous Skin Prick Tests

Skin prick test to cow's milk and other allergens listed in Table 1 were performed using the DermaPIK device (Greer Laboratories, Lenoir, NC). The longest diameters of induration and flare were measured after a 15-minute time interval.

CAP Radioallergosorbent Test

ImmunoCAP radioallergosorbent test (RAST; Pharmacia AB, Uppsala, Sweden) to food allergens, including cow's milk, beef, chicken, egg white, peanut, and shrimp, was performed.

Atopy Patch Tests

Atopy patch tests were performed using saline, nonfat milk (20 µg) in saline, milk in petroleum, and petroleum.

Double-Blind, Placebo-Controlled Oral Challenge

After 2 weeks on elimination diet with avoidance of all milk-containing products and avoidance of antihistamines for

Table 1. Epicutaneous Prick Tests and CAP Radioallergosorbent Test (RAST) Results*

Allergen	Induration at 2.5 months old, mm	Induration at 13 months old, mm	Induration at 23 months old, mm	CAP RAST, kU/L/class at 23 months old
Cow's milk	3†	4†	6†	>100/VI
Beef	X	8	8†	55/V
Chicken	X	8†	0	1.1/II
Egg white	X	12†	8†	36/IV
Egg yolk	X	7†	4†	X
Peanut	X	7†	3†	96/V
Shrimp	X	9†	8†	26/V
Yogurt	X	X	4†	X
Diluent	N	N	N	X
Histamine	2	7	6	X

Abbreviations: N, nonreactive response; X, test not performed.

*Skin prick testing and CAP RAST to food allergens were performed. This patient was allergic to multiple foods, with the largest response to cow's milk on CAP RAST. Total serum IgE level at 23 months was 12,150 kU/L. CAP RAST to inhalants revealed class III responses to fescue and Timothy grass and class I and II responses to other inhalants tested.

† Clinical relevance with worsening rash after consumption of the food.

10 days, double-blind, placebo-controlled oral challenge to cow's milk was performed. Grape juice (placebo) or escalating doses of nonfat dry milk (0.5, 1, 2, 4, and 8 g, mixed in 20 to 100 mL of grape juice) were given at 30-minute intervals. Grape juice alone was well tolerated.

CASE REPORT

This patient is a male infant born at 40 weeks' gestational age by normal, spontaneous, vaginal delivery with a birth weight of 3,814 g, length of 48 cm, and Apgar indices of 8 and 9. He presented at 6 hours of age with respiratory distress and cyanosis, requiring mechanical ventilation and surfactant. Chest radiography revealed a right upper lobe infiltrate and ground glass appearance of the lungs, although blood and tracheal aspirate cultures were negative. Initial laboratory studies revealed a circulating eosinophil count of 410/mm³ that increased to 665/mm³ at 5 days. He received 7 days of empiric antibiotics and showed clinical improvement. He was discharged at 1 week of age.

At 3 weeks of age, he presented with an erythematous, crusted rash localized to the face and scalp. He was treated with oral cephalexin, Nystatin (Bristol-Myers Squibb, Princeton, NJ), and oatmeal baths for 5 days. His initial circulating eosinophil count was 13,800/mm³, increasing within 2 weeks to a total leukocyte count of 76,300/mm³ with 58% eosinophils. He was readmitted at 5 weeks with a generalized maculopapular, papulovesicular rash on his face, scalp, back, neck, and chest. The lesions had foul-smelling, yellow discharge. He had normal activity, normal appetite, and no associated fever. He was hospitalized for treatment with ceftriaxone for 3 days and completed a 1-week course of Nystatin and Selsun Blue (Chattem Inc, Chattanooga, TN). Within 4 days, the skin lesions were nearly resolved. Skin potassium hydroxide test result was negative. Viral cultures and direct fluorescence antibody to herpes simplex results were negative.

Despite treatment with Lotrimin (Schering-Plough, Kenilworth, NJ) and hydrocortisone creams, the child was readmitted with worsening rash and FTT at 10 weeks of age (Fig 1). From birth to 10 weeks of age, his weight percentile had dropped from 90% to 5%, and length dropped from 10% to below the fifth percentile. Skin biopsy revealed a perifollicular and periadnexal mixed cell infiltrate of histiocytes,



Figure 1. Infant with hyper-IgE syndrome with recalcitrant dermatitis. Diffuse skin lesions are seen on the face and scalp. Prominent forehead with frontal bossing is shown. Skin biopsy confirmed the diagnosis of eosinophilic pustular folliculitis.

eosinophils, and neutrophils, consistent with eosinophilic pustular folliculitis. Lymphocyte cell surface markers revealed 8% CD19+ B cells and 80% CD3+ T cells with 5% activated T cells. He had 63% CD4+ T cells and 20% CD8+ T cells with 2% natural killer cells. Mitogen responses to phytohemagglutinin and concanavalin A were normal, with response to pokeweed mitogen 26% that of control. His circulating eosinophil count was 6,310/mm³ with an IgE level of 8,454 U/mL. Serum immunoglobulin levels were an IgG reading of 754, IgA of 72, and IgM of 112 mg/dL. At 3 months of age, IgD was less than 1.5 mg/dL. Chromosome test results were normal.

Allergy skin prick test to cow's milk revealed a 3-mm induration in the presence of a negative control. Histamine control showed a 2-mm induration (Table 1). While hospitalized, he was treated with oxacillin. He was discharged with cephalexin for prophylaxis and treatment, Benadryl (Pfizer Consumer Healthcare, Morris Plains, NJ), hydrocortisone cream 2.5%, and Westcort 0.25% cream (Bristol-Myers Squibb) to the face.

After change from Similac with iron to an amino acid-based formula (Neocate; SHS North America, Gaithersburg, MD), his rash improved markedly within 10 days, and he showed steady improvement in growth with an average weight gain of 30 g/d for the subsequent 2 months. This clinical improvement was accompanied by a decrease in both IgE level to 2,747 U/mL and circulating eosinophil count to 2,100/mm³. At 3 months of age, econazole nitrate 1% cream was added as empiric treatment. His skin remained clear of rash (Fig 2) until he was introduced to yogurt and other table foods. When exposed to yogurt, eggs, chicken, turkey, shrimp, fish, peanut, or beef, however, his skin lesions flared. Avoidance of these foods led to improvement of the skin lesions, which supports the clinical significance of his food allergies as an etiology of his skin lesions. Repeat skin prick

testing was performed at 13 and 23 months and revealed positive responses to all of these foods (Table 1). Avoidance of chicken, because of flaring of his skin lesions, from the age of 13 months for the following 10 months, led to a negative skin prick test result at 23 months. During the few months that he ate yogurt several times a week, his skin lesions worsened. Subsequent avoidance of yogurt led to improvement of his skin lesions. Specific IgE level to cow's milk measured by Immuno CAP RAST was greater than 100 kU/L, class VI. Total serum IgE level at the time was 12,150 kU/L. Atopy patch tests were also performed to support the diagnosis of cow's milk allergy. Within 48 hours of application of atopy patch tests, papules (+, weak positive reaction) were seen at the sites with milk in saline and milk in petroleum. As shown in Figure 3, pruritic, erythematous skin lesions with excoriations of his chin developed within 48 hours of cow's milk challenge.

At 15 months, nail hyperkeratosis was noted, although skin test results for potassium hydroxide were negative (Fig 4). An attempt at discontinuing prophylactic antibiotics resulted in 3 cold abscesses on his scalp, as well as multiple pustular lesions at the hairline and shoulders within 2 weeks. The lesions resolved once cephalexin was resumed. He has remained clinically well while taking cephalexin, with the exception of 1 episode of barking cough associated with fever. Chest films revealed a right upper lobe infiltrate, which responded to a 1-week course of ceftriaxone.

Family history is significant for paternal asthma and allergic rhinitis. His father had multiple allergies to pollen, mold, and dust, as well as shrimp and crab allergy as a young man. Environmental history was unremarkable.

DISCUSSION

We report a case of cow's milk allergy associated with hyper-IgE syndrome and the benefit of treatment for cow's milk allergy. Treatment with an amino acid-based elemental formula, in conjunction with antistaphylococcal therapy, re-



Figure 2. Skin lesions improved during treatment with oral antibiotics in combination with Neocate formula in this child with hyper-IgE syndrome and cow's milk allergy.



Figure 3. Development of pruritic, erythematous skin lesions with excoriations within 48 hours of double-blind, placebo-controlled milk challenge.



Figure 4. Toenails with hyperkeratosis in this patient with hyper-IgE syndrome. The results were negative for potassium hydroxide. The findings worsened after the child started walking.

sulted in dramatic improvement of recalcitrant eosinophilic folliculitis and life-threatening FTT. Since delayed growth may be seen in both hyper-IgE syndrome and cow's milk allergy,¹⁻³ the need to address both diseases in this patient was essential. The diagnosis of cow's milk allergy in this patient is supported by his dramatic clinical improvement on elemental formula, flare of dermatitis when exposed to yogurt, and positive epicutaneous skin prick test result, CAP RAST to cow's milk (>100 kU/L, score VI), and double-blind, placebo-controlled milk challenge. The diagnosis of hyper-IgE syndrome in this patient is supported by the early onset of the papular characteristic rash, extreme fluctuation of IgE and circulating eosinophil count, cold abscesses while not using antistaphylococcal therapy, finger and toe nail hyperkeratosis, and recurrent pneumonia.

Hyper-IgE syndrome is characterized by elevated serum IgE levels, recurrent staphylococcal infections, and dermatitis. Hyper-IgE syndrome is seen in both males and females. In a series of 9 patients described by Leung and Geha,¹ all had the first manifestations of disease, either as dermatitis or infections, by 6 weeks of age. All patients had papular skin lesions of the face and extensor surfaces. Serious infections occurred more commonly after 6 months of age, most frequently due to *Staphylococcus aureus*. Other studies have described deep-seated infections, including recurrent bacterial arthritis or osteomyelitis.^{2,4,5} Abscesses of the lungs, often leading to pneumatoceles, or the skin, particularly the scalp, face, or neck, are common. Over half of the patients had recurrent nail, mucosal, or skin infections with *Candida*. Other features described in patients with hyper-IgE syndrome consist of coarse facial features, including a prominent forehead, broad nasal bridge, facial asymmetry, growth retardation, osteoporosis often associated with fractures, scoliosis, hyperextensible joints, conjunctivitis and corneal ulcerations, and retained primary teeth.^{2,4-8} An autosomal dominant form of hyper-IgE syndrome has been localized to chromosome 4q21.⁹

In addition to the elevated IgE and recurrent infections, chronic dermatitis is characteristic of hyper-IgE syndrome. Differentiating the skin lesions in atopic dermatitis from the chronic dermatitis in hyper-IgE is important, since many patients may be mistakenly diagnosed as having atopic dermatitis. Both atopic dermatitis and the dermatitis associated with hyper-IgE may be associated with extremely elevated

levels of IgE.¹ The differences between patients with hyper-IgE syndrome and those with atopic dermatitis are well described by Leung and Geha.¹ In patients with atopic dermatitis, flexural skin lesions are common, as is history of allergic conditions. Superficial *S aureus* infections occur, and onset of disease occurs after 2 months of age. In contrast, patients with hyper-IgE syndrome rarely have allergic conditions, frequently have serious, deep infections with *S aureus*, commonly have infection with other microbes, including *Candida*, Gram-negative organisms, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, and usually have onset by 6 to 8 weeks of age. Patients with hyper-IgE syndrome and food allergy do not have atopic dermatitis; instead, the chronic dermatitis associated with hyper-IgE syndrome is worsened by consumption of foods to which they are allergic.

Detailed descriptions of the nature of the food allergy and the effect of treatment for the food allergy in patients with hyper-IgE syndrome have not been reported. Since this patient's skin lesions began at 3 weeks of age and were treated with intermittent antibiotics with subsequent diagnosis by 10 weeks of age, this may have helped to prevent the development of serious deep-seated infections. Skin biopsy may be needed for definitive diagnosis to distinguish between atopic dermatitis and hyper-IgE syndrome. By skin biopsy, patients with hyper-IgE also may be evaluated with eosinophilic pustular folliculitis, as seen in our patient.^{6,10}

Food allergy manifests itself in different forms. Allergy to cow's milk can present through gastrointestinal, respiratory, or cutaneous symptoms. Often, it exacerbates atopic dermatitis. Severity of atopic dermatitis has been described using the Scoring of Atopic Dermatitis index, which takes into account the degree of erythema, edema, oozing, excoriations, lichenification, and dryness.¹¹ Using the Scoring of Atopic Dermatitis index, at the time of diagnosis, our patient had a score of 64.4 (scale of 0 to 103), which is greater than the extent of involvement, intensity, and degree of pruritus associated with atopic dermatitis in 80% of 88 patients described in the study. In this patient with hyper-IgE syndrome, food allergy led to worsening dermatitis.

The diagnosis of food allergy can be made in different ways. The gold standard for the diagnosis of food allergy is careful history taking, screening by epicutaneous allergy testing, and/or CAP RAST, followed by a double-blind, placebo-controlled food challenge.¹² The threshold CAP RAST to cow's milk protein for predicting clinical reactivity, with greater than 95% certainty, has been reported at 32 kU/L, a fraction of the specific IgE to cow's milk in this case (>100 kU/L).¹³ Although patients with hyper-IgE syndrome may have elevated IgE to specific food allergens due to their increased total IgE, the positive skin test results in our patient correlated with clinical symptoms and supported the diagnosis. The results of a double-blind, placebo-controlled challenge also confirmed cow's milk allergy in our patient.¹⁴ Our patient also frequently ate yogurt that subsequently led to flare-up of dermatitis. This clinical reaction to yogurt was supported by a positive epicutaneous prick test result (Table

1). Avoidance of yogurt led to improvement of his skin lesions. In patients with atopic dermatitis and food allergy, the use of atopy patch tests with skin prick tests has been useful in the early diagnosis of cow's milk allergy. Atopy patch tests were positive in 89% of patients with atopic dermatitis and delayed onset reactions to cow's milk.¹⁵ To further support the diagnosis of cow's milk allergy in this patient, atopy patch test was performed, and the result was positive. This supports the possibility that our patient with hyper-IgE syndrome may also have a T-cell-mediated reaction to cow's milk. Since amino acid formulas have been evaluated for safety in patients with cow's milk allergy and found to promote growth, Neocate was the formula of choice for this patient.^{3,16-18}

Immune studies in patients with hyper-IgE syndrome are variable. Eosinophilia is common both in serum and in tissues.^{1,2,8} Polymorphonuclear chemotaxis, initially believed to explain recurrent infections in patients, may be abnormal in some patients, although most patients have normal chemotaxis.^{2,5,19} Levels of serum immunoglobulins A, G, and M are usually normal, as are complement levels and mitogen responses.⁸ Serum IgE can range from 210 to 90,000 IU/mL.^{1,2} Another explanation for recurrent deep-seated infections is likely due to poor antibody production to a surface polysaccharide antigen, teichoic acid, on *S aureus*.¹⁹ Studies have shown that responses to *Candida* and diphtheria toxoid are frequently low.^{2,6,19} Antibody responses to capsular polysaccharide *H influenzae*, both preimmunization and postimmunization, were significantly lower in patients with hyper-IgE, as compared with both normal controls and patients with atopic dermatitis.¹⁹ Most patients had IgG subclass 2 deficiency. The patients also had poor responses to tetanus toxoid. Another study²⁰ investigated the antibody response to bacteriophage X174 revealing abnormal secondary antibody responses. This defective antibody production to polysaccharide, protein, and viral DNA may explain some of the difficulties patients have with recurrent infections.

Treatment of hyper-IgE begins with prophylactic antibiotics.¹ If abscesses develop, incision and drainage are often needed. In extreme cases, more aggressive options should be considered. A study²¹ using intravenous immunoglobulin in 1 patient with hyper-IgE revealed intravenous immunoglobulin did not significantly decrease IgE levels or change RAST. Plasmapheresis has been tried, with temporary relief, in a patient whose vision was threatened due to corneal ulcerations despite aggressive in-hospital treatment over 4 months.¹ Early diagnosis is most important to minimize potential sequelae from serious deep-seated infections.² Dermatitis can be treated with topical steroids. Antihistamines are useful for the treatment of pruritus. Alternative treatment modalities have been investigated. Since IgE production occurs via communication between receptors and ligands located on activated T cells and B-lymphocytes, as well as from cytokines such as interleukin 4 (IL-4) or IL-13, which can cause immunoglobulin switching from IgM to IgE, these are potential targets for therapy.²² Interferon γ has been used in some

patients as alternative therapy in hyper-IgE syndrome.²³ However, studies investigating the effect of cytokines or antibodies to cytokines on IgE production have been controversial. In a study by Vercelli et al,²² no difference in production of IL-4 by patients with hyper-IgE, as compared with controls, was seen. Antibodies to IL-4 and IL-6 did not decrease IgE production by peripheral blood mononuclear cells. These findings were challenged by a later study by Garraud et al.²⁴ In this study, IL-6 slightly increased IgG4 production, whereas no increase was seen when IL-4 or IL-13 was given. IL-12 and interferon γ each significantly reduced IgE production. Anti-IL-4 and anti-IL-3 antibodies were shown to significantly decrease production of IgE and IgG4. Antibodies to IL4 receptor, as well as IL-8, anti-IL-6, and anti-tumor necrosis factor α antibodies, inhibited IgE and IgG4 production completely.²⁴ The current report suggests that food allergy may be one of the triggering factors for the overproduction of IgE in some patients with hyper-IgE syndrome.

CONCLUSION

The phenotypes of hyper-IgE syndrome are diverse. New therapeutic modalities are being investigated for the treatment of hyper-IgE. This is the first report of a patient with hyper-IgE syndrome and cow's milk protein allergy in whom Neocate formula, in combination with traditional prophylactic antistaphylococcal antibiotics, was effective in treating FTT. We recommend the consideration of food allergy in patients with hyper-IgE syndrome who partially respond to traditional therapy.

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