

Release of inflammatory mediators after cow's milk intake in a newborn with idiopathic pulmonary hemosiderosis

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Idiopathic pulmonary hemosiderosis (IPH) is characterized by repeated episodes of intraalveolar bleeding, hemosiderin deposition in alveolar macrophages, and subsequent development of pulmonary fibrosis and severe anemia.¹ This disease predominantly affects children; the age of occurrence ranges from 4 months to 62 years, although cases in newborn infants have been described.² The pathologic mechanism is not well understood, but some evidence supports an immunopathologic basis.¹

The association of IPH with hypersensitivity to cow's milk proteins was first reported by Heiner and Sears³ who described patients with recurrent pulmonary disease, changing roentgenographic manifestations, hemoptysis, iron-laden macrophages in gastric or bronchial washings, iron deficiency anemia, and multiple precipitins to cow's milk. Additional studies have shown peripheral blood eosinophilia; alveolar deposits of IgG, IgA, and C3; circulating immune complexes; and delayed hypersensitivity to cow's milk proteins.^{4,5}

We studied a newborn infant with IPH and myocardial involvement in whom the administration of cow's milk proteins induced peripheral eosinophilia and the release of histamine and eosinophilic cationic protein (ECP) in peripheral blood and bronchoalveolar lavage (BAL) and the release of histamine in urine.

CASE REPORT

A 5-day-old boy was attended in the emergency department of our hospital after an episode of vomiting with

Abbreviations used

BAL:	Bronchoalveolar lavage
ECP:	Eosinophil cationic protein
IPH:	Idiopathic pulmonary hemosiderosis
NMH:	N-methyl histamine

blood after cow's milk feeding. He was released after the family refused to allow a study. Twelve days later, he was admitted to the intensive care unit with bradycardia of 20 beats/min, gasping, severe cyanosis, and respiratory failure. The patient required mechanical ventilation. BAL analysis showed abundant macrophages loaded with hemosiderin deposits. The differential cell count was 37% macrophages, 70% granulocytes, and 10% mononuclear cells. X-ray examination revealed a bilateral interstitial alveolar infiltrate. Echocardiographic study disclosed restrictive myocardiopathy with mitral valve involvement. Blood analysis revealed anemia (hemoglobin, 8.6 gm/dl; hematocrit, 25.7%) and peripheral eosinophilia (total cell count, 2616). Immunoglobulin levels were: IgG, 341 mg/ml; IgA, 23 mg/ml; IgM, 108 mg/ml; and IgE, 37 KU/ml. IgG-specific antibodies determined by ELISA to cow's milk proteins (α -lactoalbumin, β -lactoglobulin, and casein) were not detectable. IgE-specific antibodies to cow's milk proteins (β -lactoglobulin, and α -lactoalbumin, and casein) were not detected. T lymphocytes CD4, CD3, CD8, and the CD4/CD8 ratio were within normal limits. Results of urine analysis were normal, and no parasites were found in the stool.

During the patient's stay in the intensive care unit, it was observed that when he was fed with a non-milk formula by enteral nutrition, the red blood cell count increased (hemoglobin, 16.4 gm/dl; hematocrit, 49.2%), and the eosinophils decreased to 200 cells/mm³. However, peripheral anemia and eosinophilia, similar to the values described previously, were observed when the patient was started on a milk diet by enteral nutrition.

The involvement of cow's milk proteins in the triggering of the abnormalities described in this report was studied by a controlled challenge. The subject was fed on one day with milk substitute and on a different day with

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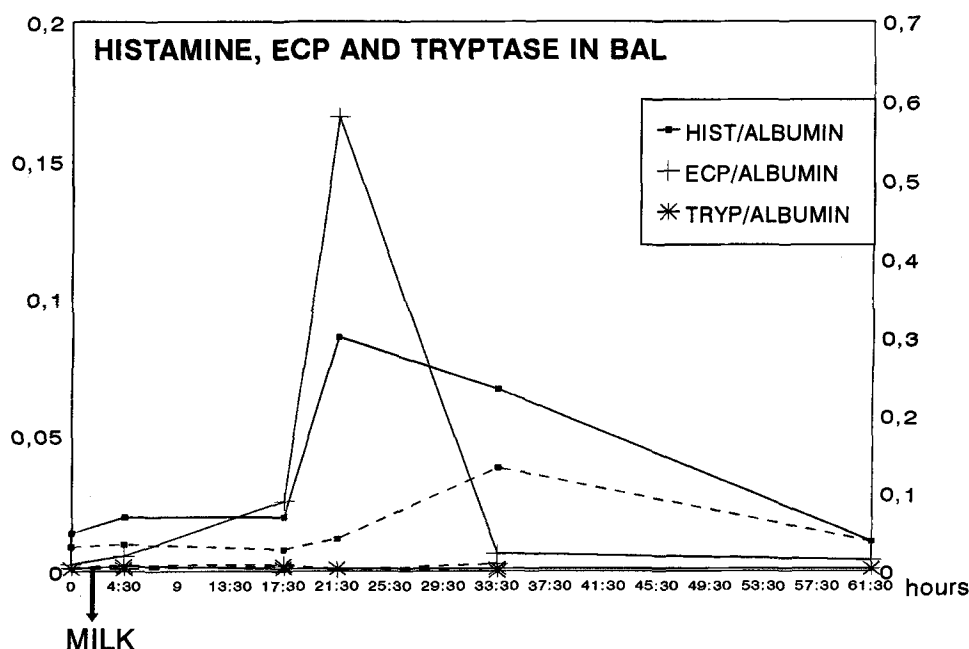


FIG. 1. Evolution of inflammatory mediators in BAL during and after placebo (dotted lines) and cow's milk (solid lines) challenges.

cow's milk formula. The following inflammatory mediators and cell markers were quantified: histamine, tryptase, and ECP in blood and BAL and N-methylhistamine (NMH) in urine. Nineteen hours after challenge with milk, there was a histamine peak 6.1 times the prechallenge level (histamine/albumin = 0.086) and an ECP peak 64.4 times (ECP/albumin = 0.58) the prechallenge level in BAL. ECP returned to initial value 27 hours after challenge, and histamine returned to initial value 55 hours after challenge. Tryptase was below detectable limits during the study period (Fig. 1). The blood levels of histamine (120 ng/ml) peaked 9 hours after the milk challenge, and levels of ECP (35.4 μ g/ml) peaked 46 hours after the milk challenge. Tryptase levels in blood were below detectable limits in all the serum samples during the study period (Fig. 2). The total eosinophil count in peripheral blood during this period peaked at 46 hours (baseline level, 50; 46 hours, 850). The hematocrit was within normal limits before milk challenge but was markedly decreased 8 hours after cow's milk challenge (baseline level, 46.7%; 8 hours, 25.8%). The NMH excretion in urine peaked 10 hours (NMH/creatinine = 23.42) after the milk challenge and returned to baseline values in 32 hours (Fig. 3). Sequential measurements of inflammatory mediators taken at the same intervals after administration of non-milk enteral nutrition did not show any histamine or ECP peaks in BAL or peripheral blood or any NMH peak in urine at the corresponding times of the peaks after administration of cow's milk.

DISCUSSION

The data shown in this study strongly suggest that an inflammatory response with the involvement of different cells occurred after cow's milk intake. The rise of ECP in BAL sooner than in peripheral blood indicated that the eosinophil activation occurred in the lungs. The increase of histamine indicated that mast cells and/or basophils were activated, and the nondetection of tryptase suggests that no anaphylactic response took place. The study of the inflammatory markers in blood showed that the histamine peaked at the same time as in BAL, whereas the blood ECP levels increased at a rather delayed interval compared with the BAL ECP levels.

The pathologic mechanisms of milk allergy are complex. Two main mechanisms, type I (immediate) and type IV (delayed), are involved in the induction of these reactions. In immediate reactions subjects have IgE antibodies to milk proteins and positive immediate skin test results, and their cells often release histamine after milk exposure. In delayed reactions patients more often have positive responses to epicutaneous tests and also have lymphocyte proliferation to milk allergens.⁶ Kondo et al.⁷ suggested that in subjects with atopic dermatitis and food sensitivity, both immediate and delayed reactions may occur. In these patients

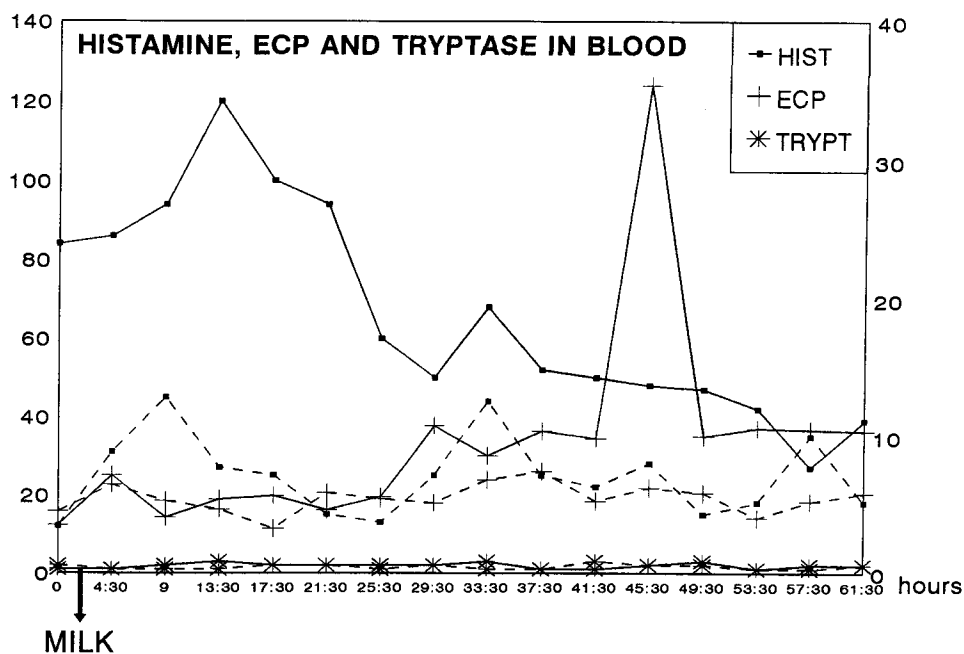


FIG. 2. Evolution of inflammatory mediators in blood during and after placebo (dotted lines) and cow's milk (solid lines) challenges.

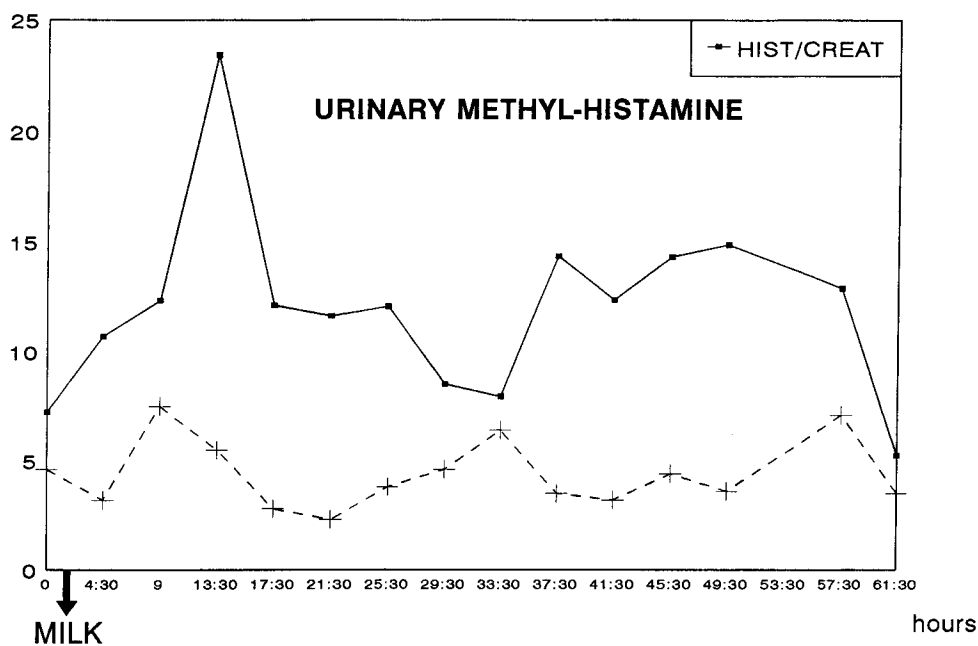


FIG. 3. Evolution of NMH in urine during and after placebo (dotted lines) and cow's milk (solid lines) challenges.

CD4 T lymphocytes stimulated by food allergens release IL-2 and interferon- γ , a pattern of T_{H1} clones, and they also express Fc ϵ RII on B lymphocytes, induced by IL-4, a pattern of T_{H2} clones. In the patient described in this report, the time elapsed between the administration of milk and

the peak of the inflammatory markers indicates that a delayed immune response took place. The lack of IgE antibodies to milk proteins, the absence of increased levels of tryptase, and the nonoccurrence of immediate symptoms after cow's milk challenge rule out an IgE-mediated mechanism.

Although the activation of eosinophils by cytokines has been reported^{8,9} and several authors have found increased lymphocyte proliferation to food antigens in patients with food allergy,¹⁰ these data have not yet been reported in patients with pulmonary hemosiderosis. We propose that in this case a specific activation mechanism in sensitized T cells may have taken place and these cells may have released cytokines that activate eosinophils, basophils, and/or mast cells. Therefore in patients with IPH in whom milk allergy may trigger or aggravate pulmonary damage, controlled administration of milk proteins with quantitation of different inflammatory mediators may help to establish a causal relationship.

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Previously undiagnosed hyper-IgE syndrome in an adult with multiple systemic fungal infections

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First described in 1966 in two red-haired girls with recurrent "cold" staphylococcal abscesses,¹ hyper-IgE (Job's) syndrome is a rare, complex immunoregulatory disorder characterized by elevated serum IgE levels,² eczematoid dermatitis, and recurrent bacterial infections.^{3,4} The infections begin early in life and consist of recurrent skin infections, otitis media, sinusitis, and pneumonia. The major bacterial pathogen is *Staphylococcus aureus*, and less commonly *Haemophilus influenzae*, streptococci, or enteric bacteria. Nonbacterial infections, particularly

mucocutaneous candidiasis, also occur; but systemic fungal infections are unusual.⁵

Most patients with hyper-IgE syndrome are diagnosed in childhood. We describe a patient with hyper-IgE syndrome who, despite all the classical features, remained undiagnosed until adulthood when he was first seen with multiple systemic fungal infections.

CASE REPORT

A 38-year-old man was referred to Baylor College of Medicine for evaluation of multiple systemic fungal infections. The patient had a history of eczematous skin rashes from the age of 3 weeks, severe ear infections starting at 3 months, severe acne from the age of 1 year, recurrent sinusitis beginning at 12 years (status after 2 Caldwell-Luc operations with bilateral ethmoidectomies), septic arthritis of the right hip as a result of staphylococcus at 16, and multiple episodes of pneumo-

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