

Case Report

Milk-induced pulmonary disease in infants (Heiner syndrome)

Moissidis I, Chaidaroon D, Vichyanond P, Bahna SL. Milk-induced pulmonary disease in infants (Heiner syndrome). *Pediatr Allergy Immunol* 2005; 16: 545–552. © 2005 Blackwell Munksgaard

Heiner syndrome (HS) is a food hypersensitivity pulmonary disease that affects primarily infants, and is mostly caused by cow's milk (CM). Only a few reports have been published, which may be due to its misdiagnosis. We review here a series of eight cases. When first diagnosed they were 4–29 months of age. They were fed CM from birth and their chronic respiratory symptoms began at age 1–9 months. The symptoms were in the form of cough in seven, wheezing in three, hemoptysis in two, nasal congestion in three, dyspnea in one, recurrent otitis media (OM) in three, recurrent fever in four, anorexia, vomiting, colic or diarrhea in five, hematochezia in one, and failure to thrive (FTT) in two. All had radiologic evidence of pulmonary infiltrates. High titers of precipitating antibodies to CM proteins were demonstrated in six of six and milk-specific immunoglobulin E (IgE) was positive in one of two. Pulmonary hemosiderosis (PH) was confirmed in one patient who showed iron-laden macrophages (ILM) in the bronchoalveolar lavage (BAL), gastric washing, and open lung biopsy. Additional findings, in a descending frequency, were eosinophilia, anemia, and elevated level of total IgM, IgE or IgA. Milk elimination resulted in remarkable improvement in symptoms within days and clearing of the pulmonary infiltrate within weeks. Parents consented to milk challenge in only three cases, all of whom developed recurrence of symptoms. After 2 yr of milk avoidance in one patient, milk challenge was tolerated for 2 months, and then the patient developed symptoms, serum milk precipitins, pulmonary infiltrate, and ILM. The HS should be suspected in young children with chronic pulmonary disease of obscure cause. The diagnosis is supported with a positive milk precipitin test and improvement on a trial of milk elimination. Severe cases may be complicated with PH, which should be suspected in the presence of anemia or hemoptysis and be confirmed with the demonstration of ILM.

Ioannis Moissidis¹, Darunee Chaidaroon², Pakit Vichyanond² and Sami L. Bahna¹

¹Allergy and Immunology Section, Louisiana State University Health Sciences Center, Shreveport, LA, USA, ²Siriraj Hospital, Mahidol University, Bangkok, Thailand

Key words: Heiner syndrome; pulmonary disease; pneumonia; food allergy; cow's milk

Sami L. Bahna, Allergy and Immunology Section, LSUHSC Department of Pediatrics, 1501 Kings Highway, Shreveport, LA 71130-3932, USA
Tel.: (318) 675-7625
Fax: (318) 675-8815
E-mail: sbahna@lsuhsc.edu

This paper has been presented in part at the World Allergy Organization Congress – XVIII ICACI, September 7–12, 2003, Vancouver, Canada.

Accepted 9 September 2004

Since the discovery of the milk-induced pulmonary syndrome, more than 40 yr ago (1), only a few reports have been published (2–4). The syndrome is probably rare, but as it has no pathognomonic features, it is likely to be misdiagnosed. The most common manifestations are listed in Table 1.

Case reports

We describe eight cases, five males and three females, age 4–29 months when diagnosed. All

patients had chronic or recurrent lower respiratory symptoms that did not resolved with the usual therapeutic measures (cough medications, antibiotics, decongestants).

The clinical and laboratory findings on each of the eight patients are presented in Table 2. Because the cases were evaluated at different times and under different circumstances, certain data were not available in every case. To illustrate the course of the disease, three case reports are presented.

Table 1. Manifestations of milk-induced chronic pulmonary disease (Heiner syndrome)

Chronic or recurrent lower respiratory symptoms often associated with upper respiratory symptoms, gastrointestinal symptoms, and failure to thrive
Chest roentgenograph may show patchy infiltrates, localized atelectasis, consolidation, peribronchial infiltrate, hilar adenopathy, pleural thickening, or reticular density
Some patients may have eosinophilia and iron deficiency anemia
Serum precipitating antibodies to multiple cows' milk protein fractions
Pulmonary hemosiderosis in some cases
Resolution on cow's milk-free diet

Patient 1

A 23-month-old Caucasian female referred for evaluation of chronic cough and persistent upper respiratory congestion. She was born full term and fed CM formula from birth. During the first week of life, she had diarrhea and colic that improved upon switching her diet to soybean formula. She developed recurrent vomiting, persistent upper airways congestion, and chronic cough with the introduction of baby foods at the age of 4 months. Her symptoms became worse at the age of 1 yr, when homogenized milk was introduced. They include chronic nasal stuffiness frequent cough, sneezing, recurrent fever, otitis media (OM), and pneumonia. At 12 months of age her weight was at the 20th percentile. Previous treatments with antibiotics, cough syrups, and antihistamines gave only temporary relief. Tests for GE reflux and sweat chloride showed normal findings.

At 26 months of age, a trial of strict cow milk (CM) elimination was started and she was referred for further evaluation. At 27 months of age (while on milk elimination for 4 wk), the mother reported remarkable improvement in the child's respiratory symptoms within a few days and became totally asymptomatic within 2 wk without any medications.

Physical examination revealed: weight at 85th percentile, height at 50th percentile, normal vital signs, edematous and pale nasal mucosa, and minimal clear nasal discharge. Tympanic membranes were dull with poor light reflex. Tonsils were hypertrophic but not inflamed. Lungs were clear to auscultation and skin showed no rashes. Tympanogram was flat on the right side (indicating middle ear effusion) and negative pressure (-150 mm H₂O) on the left side (indicating Eustachian tube dysfunction).

Laboratory studies showed WBC 8390 cells/mm³ [polymorphonuclear cells (PMN) 57%, lymphocytes 32%, monocytes 8%, eosinophils 3%], and hemoglobin (Hgb) 12.9 g/dl (was 11 g/dl before milk avoidance). Percutaneous allergy testing was negative to whole CM, casein, whey,

lactalbumin, and evaporated milk. Serum total IgE level was 64 U/ml (normal: < 30 U/ml), and radioallergosorbent test (RAST) was negative to IgE antibodies to CM.

Chest roentgenograms on multiple occasions from the age of 13 months showed shifting bilateral infiltrates with partial clearing between clinical exacerbations, but never completely clear while on a milk-containing diet. The chest X-ray film just before milk elimination showed bilateral perihilar infiltrates and right middle lobe atelectasis (Fig. 1a). It took almost 8 wk for the chest X-ray film to be clear. At 2 months, the tympanometry showed marked improvement on the right side and became normal on the left side.

With some persuasion, the family agreed to a milk challenge test. The child appeared to tolerate gradual reintroduction of CM on an almost daily basis and the chest X-ray film remained clear 4 wk through the challenge (Fig. 1b). At 5 wk the patient developed upper respiratory symptoms and the chest X-ray film showed bilateral infiltrate (Fig. 1c). The patient's symptoms completely resolved shortly after CM avoidance, without any medications.

The serum was tested for CM precipitating antibodies by double immunodiffusion in agar (micro-Ouchterlony technique) (5) on two occasions. While the child was on a milk elimination diet for 1 month, the test was moderately positive and became strongly positive following reintroduction of milk and recurrence of symptoms (Fig. 2).

Patient 2

A 19-month-old African-American male was referred for evaluation of chronic upper and lower respiratory tract symptoms. He had a history of recurrent fever, OM, and recurrent pneumonia since 4 months of age. There were also episodes of abdominal pain and recurrent mild urticaria since 2 months of age. Serial chest X-ray films between 4 and 22 months of age (total 12) showed a wide variety of findings, including mild pneumonitis, pneumonia, linear perihilar infiltrates, fibrotic changes, and opacities in different lung lobes.

Laboratory studies showed normal WBC with differential and iron deficiency anemia (Hgb 9–10.6 g/dl) since late infancy. At 16 months of age, his serum immunoglobulin levels were normal for IgG (900 mg/dl), IgM (246 mg/dl), and IgA (178 mg/dl), but elevated for IgE (570 IU/ml). At 19 months, serum milk precipitating antibodies test showed five precipitate lines. On two occasions, morning gastric aspirate was

Table 2. Clinical and laboratory findings on eight patients with Heiner syndrome

Patients/methods	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age/sex	27 months/F	19 months/M	14 months/F	12 months/M	4 months/M	18 months/M	15 months/M	29 months/F
Initial diet	Cow's milk	Cow's milk	Cow's milk	Multiple form	Cow's milk	Cow's milk	Cow's milk	Cow's milk
Age of onset	4 months	4 months	2 months	1 month	1 month	9 months	Infancy	5 months
Symptoms								
Upper respiratory	Congestion rhinorrhea	Nasal congestion	Nasal congestion	NA	Rhinorrhea	NA	NA	NA
Lower respiratory	Cough	Cough	Wheeze	Wheeze	Cough	Cough	Cough, hemoptysis	Cough, hemoptysis
Gastrointestinal	Vomiting	Diarrhea	Diarrhea, thrush	Vomiting	Diarrhea	Vomiting	Vomiting, diarrhea	
Other	Urticaria	Urticaria	FTT		FTT, Guaiac+			
Auscultation	Clear	Rhonchi, wheeze	Crackles, wheeze	Wheeze	Crackles	Crackles	Crackles	Hypoxia
Fever	Yes	Yes	Yes	Yes	Yes	Yes	NA	Wheeze
Infections	OM, pneumonia	URI/OM/pneumonia OM, bronchiolitis	OM, bronchiolitis	NA	Pneumonia	Pneumonia	Pneumonia	Pneumonia
Effect of milk elimination	Improvement	Improvement	Improvement	Improvement	Improvement	Improvement	Improvement	Improvement
Oral milk challenge	Positive	Positive	ND	ND	ND	ND	ND	Positive
Laboratory studies								
Milk allergy ST	Positive (2+)	ND	ND	ND	ND	ND	ND	Negative
Milk RAST	Negative	ND	ND	Positive	Negative	ND	ND	Negative
Milk precipitin test	Positive	Positive	ND	ND	Positive	Positive	Positive	Positive
Eosinophilia	Blood, nasal	Blood	Blood	Blood	NA	NA	Negative	Positive
Iron deficiency anemia	NA	Yes	MCV 60	Microcytes, hypochromic	NA	NA	Yes	No
Serum immunoglobulins	↑IgE	↑IgE, ↑IgA, ↑IgM	ND	Normal	↑IgM	ND	ND	↑IgM
Sweat testing	Negative	ND	ND	Negative	Negative	ND	ND	ND
GE reflux	Negative	ND	Negative	Negative	Negative	Positive	ND	Negative
Chest X-ray	Infiltrates	Infiltrates, fibrosis	Infiltrates	Infiltrates	Infiltrates	Infiltrates	Infiltrates	Infiltrates, ILD
ILM	ND	Negative	ND	ND	ND	ND	ND	Positive

ND, not done; NA, not available; ILD, interstitial lung disease; OM, otitis media; URI, upper respiratory infection; FTT, failure to thrive; ILM, iron-laden macrophages; RAST, radioallergosorbent test; Ig, immunoglobulin.

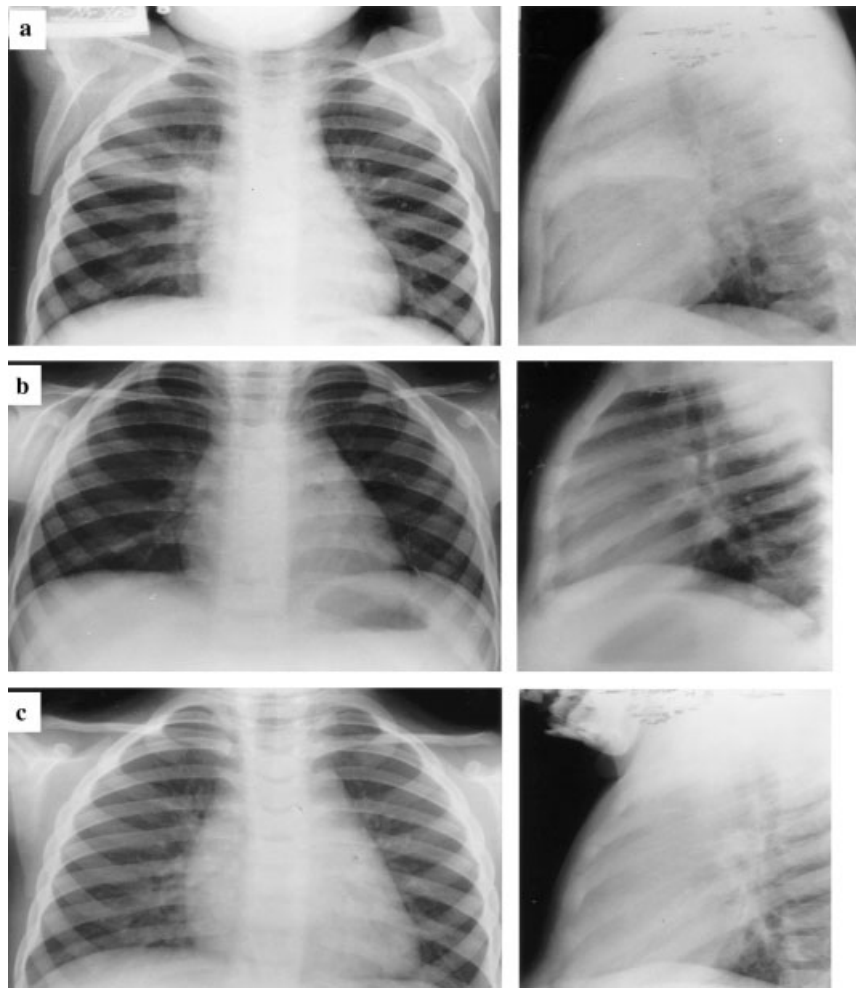


Fig. 1. Chest roentgenograms of case 1. (a) While symptomatic on milk-containing diet shows bilateral perihilar infiltrates and RML atelectasis. (b) Remains clear after 4 wk of reintroduction of cow's milk and patient still asymptomatic. (c) Recurrence of bilateral infiltrate after 5 wk of reintroduction of cow's milk and patient became symptomatic.

negative for iron-laden macrophages (ILM). Cow's milk challenge performed in the hospital for 3 days resulted in excessive diarrhea but no respiratory symptoms.

Cow's milk elimination resulted in rapid resolution of his diarrhea and within 2 months his respiratory symptoms significantly improved and further follow up was lost.

Patient 8

A 29-month-old Thai female with normal birth history was referred with a history of recurrent pneumonia, an episode of hemoptysis, and recurrent mild wheeze since 5 months of age. She was treated with antibiotics and bronchodilators with no significant improvement. At the age of 2 yr, during a hospital admission for dyspnea and pneumonia, the evaluation showed: WBC 18,600 cells/mm³ (PMN 22.7%, lymphocytes 57.9%, and eosinophils 7.7%), Hgb 12.6 g/dl, Hct 41.2%, platelets 378,000 cells/cu³. She had normal levels of IgG (1350 mg/dl), IgA (84 mg/dl), IgM (423 mg/dl), and CH50 (52 U/

ml), as well as negative PPD, and negative titers for cold agglutinin and mycoplasma. Skin prick testing with common food allergens was negative and milk-specific serum IgE was negative (<0.35 kU/l).

Sinus X-ray films showed mild bilateral maxillary sinusitis. Chest X-ray films showed bilateral upper lobe infiltrate. High resolution computed tomography (CT) showed evidence of interstitial lung disease in the right upper lobe and consolidation in both upper lobes (Fig. 3a,b). The serum was positive for precipitating antibodies to CM. BAL and gastric washing were both positive for ILM (Fig. 4a). Open lung biopsy from the left lower lobe showed alveolar hemorrhage and hemosiderosis, without fibrotic changes or vasculitis (Fig. 4b). Tissue cultures for aerobes, anaerobes and fungi were negative.

Over 3 months she received several courses of antibiotics, oxygen, bronchodilators, and systemic corticosteroids. She was also put on a milk-free diet with gradual improvement in symptoms. Within 3 months her ventilation perfusion scan

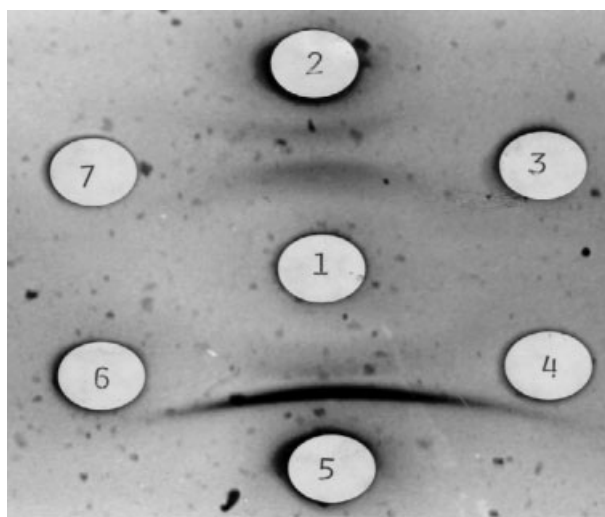


Fig. 2. Case 1: Micro-Ouchterlony test for precipitating antibodies to cow's milk demonstrating thicker precipitin lines when the patient became symptomatic after re-introduction of milk compared to those when the patient was asymptomatic on a milk-free diet for 1 month. (1) Skim raw cow's milk (antigen); (2) patient's serum while on a milk-free diet for 1 month and asymptomatic; (3) normal saline control as a negative control; (4) empty; (5) patient's serum while on cow's milk for 5 weeks and symptomatic; (6) umbilical cord serum as a negative control; (7) empty.

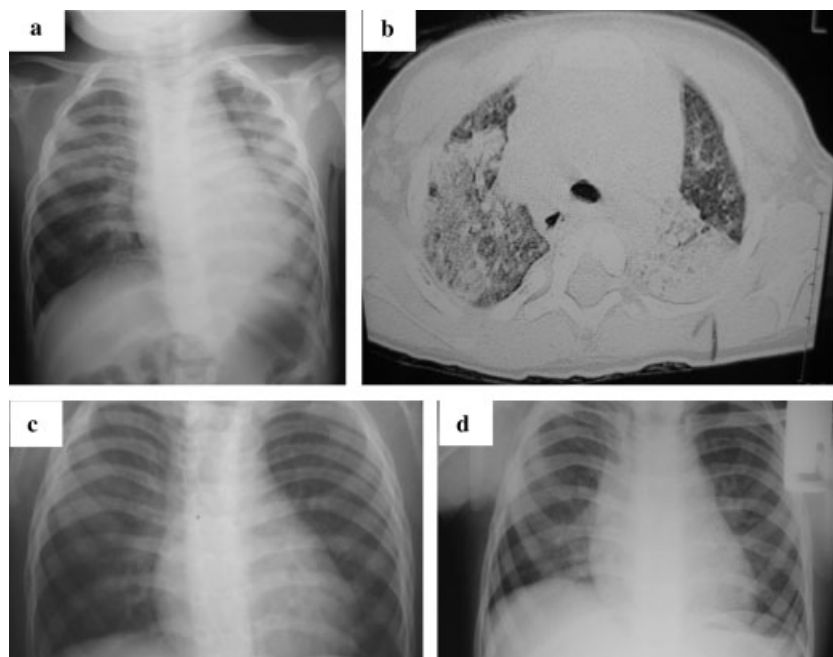
became normal and a chest X-ray film was clear (Fig. 3c). She continued free of respiratory symptoms while on a milk elimination diet for 2 yr and the milk precipitin test was negative. She was challenged with CM for 5 days but no symptoms occurred for a period of 2 wk. Cow milk was reintroduced in her diet but after

2 months, her respiratory symptoms (cough, wheezing, sputum production, and dyspnea) recurred. Her chest X-ray showed bilateral lung infiltrates (Fig. 3d), the milk precipitin test became positive, and the gastric washing showed ILM. She dramatically improved following a short course of oral steroids and a milk-free diet. The patient has been doing well in regular follow up visits.

Discussion

Milk-induced chronic pulmonary disease was first described by Heiner and Sears (1) in a group of seven children, 6 wk to 17 months old, who were on CM and had recurrent pulmonary infiltrates associated with chronic cough, recurrent fever, tachypnea, wheezing, rales, failure to thrive (FTT), and family history of allergy. Chest roentgenograms showed shifting patchy infiltrates, frequently associated with areas of atelectasis, consolidation, reticular densities, pleural thickening, or hilar lymphadenopathy. Using micro-Ouchterlony technique (slide double immunodiffusion in agar using plexiglass reservoirs), sera of all patients had multiple precipitin lines to CM proteins. A variety of other findings included chronic rhinitis, recurrent OM, gastrointestinal symptoms and eosinophilia. Four patients had hemoptysis and anemia, in which the diagnosis of pulmonary hemosiderosis (PH) was verified by the demonstration of ILM in the bronchial aspirate or in the morning gastric washing using Prussian blue stain. Most

Fig. 3. Case 8: Chest roentgenogram (a) and lung scan (b) showing bilateral upper lobe consolidation and right upper lobe interstitial disease. Clear lungs 3 months after milk elimination (c). Recurrence of bilateral infiltrate 24 months later following reintroduction of milk for 2 months (d).



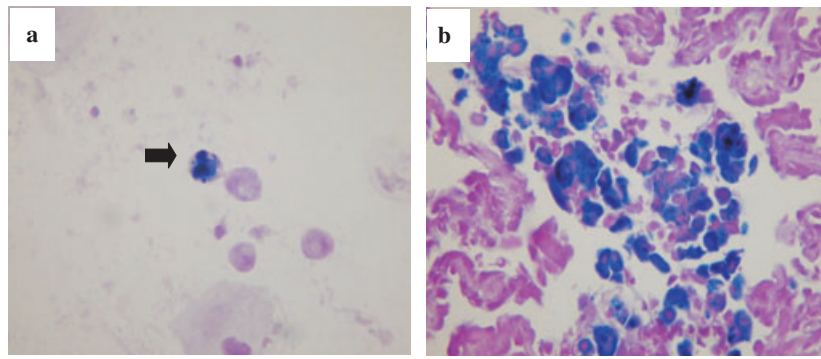


Fig. 4. Case 8: Iron-laden macrophages (Prussian blue stain) in gastric washing (a) and in an open lung biopsy (b).

symptoms strikingly decreased within a few days or weeks after CM elimination or switching to heat-treated milk.

In our series of eight patients described in this report, we believe that Heiner syndrome (HS) is the most probable diagnosis. In some patients, the medical records lacked certain information or serum was not available for testing. In such patients, the diagnosis was based on the impressive improvement in clinical and radiologic finding following milk elimination.

In food allergy in general, confirmation of the offending food is recommended by a titrated oral challenge. However, most parents of children with HS are so impressed by the dramatic improvement in symptoms and clearing of the chest roentgenograph and would not consent to a milk challenge in the child. Unlike patients with IgE-mediated food allergy, recurrence of symptoms of HS may not occur before several days to a few weeks of intake of the offending food and the symptoms can last for a long period. The risk of challenge is especially very high in patients who had hemosiderosis or had had hemoptysis. Only three of eight patients in this series consented for a challenge, and was positive in all of them.

Although HS is more likely to be induced by homogenized CM, the disease occurred in some infants fed CM-derived formula or other food proteins in older children, e.g., soy, egg, and pork (3, D. C. Heiner, personal communication). In a series by Boat et al. (2), some patients had lymphoid hypertrophy in the form of hepatosplenomegaly or hypertrophied tonsils or adenoids, and occasionally cardiomegaly or cor pulmonale.

The immunologic mechanism in milk-induced pulmonary disease is not completely clear. It probably involves the formation of immune complexes (Arthus type or Gell and Coombs' type III reaction) (6, 7). Cell-mediated reaction (Gell and Coombs' type IV) may also have a role (8). Often, more than one immunologic mechanism

is involved, and perhaps all four types of reactions are involved in certain patients (6).

Characteristically, the sera of those patients have high titers of precipitating (IgG) antibodies against bovine milk proteins, which was actually found in all six patients tested in our series. However, the presence of milk-specific IgG antibodies is not pathognomonic of the disease and can be present in low titers in sera of normal subjects ingesting milk, and in high titers in several diseases such as celiac disease, chronic diarrhea, and cystic fibrosis of the pancreas, IgA deficiency, familiar dysautonomia, Down's syndrome, Wiskott-Aldrich syndrome, and Hurler's syndrome (9, 10).

Some patients may have high serum total IgE levels, and milk-specific IgE antibodies, or circulating immune complexes (9). Elevated total serum IgE was noted in two of our patients. In some patients, the lymphocytes may show blast transformation *in vitro* on exposure to CM protein antigens (8).

The lung biopsy obtained in our patient who had hemoptysis showed alveolar hemorrhage and hemosiderosis without fibrotic changes. However, the biopsy was obtained from the left lower lobe whereas radiologically the upper lobes appeared to be more affected. It can also be attributed to an early diagnosis. Immunofluorescence studies of lung biopsy specimens from patients with milk-induced PH may show particulate and amorphous deposits of immunoglobulins, complement, fibrin, and milk protein antigens diffusely scattered throughout the lung tissue (3). In a case report of a newborn with idiopathic primary PH (IPH) and restrictive cardiomyopathy after CM feeding, quantification of inflammatory markers in the peripheral blood and bronchoalveolar lavage (BAL) showed peripheral eosinophilia and release of histamine and eosinophilic cationic protein (ECP) (11).

Bovine milk contains more than 40 separate protein fractions, each is capable of inducing

specific antibody production in humans (12). Studies, both in humans and in animals, have shown that the most allergenic CM components are β -lactoglobulin and casein, followed by α -lactalbumin, serum albumin, and γ -globulin. Regarding denaturation by heat, casein and β -lactoglobulin is the most stable, whereas serum albumin and γ -globulin are heat-labile. When the latter are the offending allergens in HS, the patients usually tolerate well heat-treated milk.

It is plausible that aspiration of milk may have a role in causing HS. Therefore, the presence of an uncoordinated swallowing mechanism, tracheal or esophageal anomaly, or gastroesophageal reflux should be ruled out. Gastroesophageal reflux was documented in one of six patients tested. Euler et al. (13), observed an increased incidence of dysfunction of the lower esophageal sphincter in children with recurrent pulmonary disease. Aspiration alone, however, cannot explain all the components of this syndrome.

In the differential diagnosis, bronchial asthma, chronic aspiration, cystic fibrosis, foreign body, hypersensitivity pneumonitis, bronchopulmonary aspergillosis, secondary PH, and IPH should be considered. The latter is a rare disorder of unknown etiology with an estimated incidence of 0.24–1.23 cases per million in some selected populations (14, 15). There is an abnormal accumulation of hemosiderin in the lungs, which results from diffuse alveolar hemorrhage (16). It may occur as a primary process in the lung or secondary to cardiac diseases, bleeding disorders, collagen-vascular disorders, or systemic vasculitis. Heiner was the first to report that some infants and young children with PH have plasma antibodies against CM (1,17). The initial presentation of IPH varies from an insidious onset of anemia, cough, dyspnea, poor weight gain, and lethargy, to a fulminant course of recurrent hemoptysis (18–20). In our third case of HS in this series, the patient had a history of recurrent pneumonia, recurrent mild wheeze, and an episode of hemoptysis. In acute hemorrhagic episodes, supportive management includes blood transfusion, oxygen therapy or mechanical ventilation (18). Corticosteroid therapy remains the first-line therapy, but in more severe cases, other immunomodulatory therapies may be helpful (hydroxychloroquine, azathioprine or cyclophosphamide) (18, 21). Without treatment, IPH leads to progressive pulmonary fibrosis and is often lethal (22).

Treatment of HS is basically strict avoidance of CM or any other identified offending food. Young children may be given a milk substitute

such as soybean formula, extensively hydrolyzed protein formula, or an elemental diet of synthesized amino acids. Indeed, all patients in our series became asymptomatic after CM elimination. Initially, symptomatic treatment, e.g., bronchodilators, antihistamines, systemic or inhaled steroids and iron may be needed, as happened with one of our patient. In cases of PH, corticosteroids, and in severe cases immunosuppressants may be tried. Cyclophosphamide was successfully used in a patient with refractory PH caused by CM (23). In general, patients with HS have better prognosis than those with IPH without milk protein hypersensitivity, and they may not need long-term immunosuppression (21). In fact, our patient with PH recovered fully within a few months of CM elimination. The prognosis is good if a milk-free diet is begun early. Most patients will be able to tolerate CM within a few years.

In conclusion, HS is worth considering in any young child with an unexplained chronic pulmonary infiltrate, an evidence of clinical allergy, and elevated levels of precipitating antibodies to bovine milk proteins in the serum. The diagnosis would be supported by documenting clinical and radiologic improvements after strict milk avoidance. The risk of verification by an oral challenge should be weighed against the benefit. Although this syndrome is rare in the general pediatric population, it should be particularly suspected in pediatric pulmonary practices. Insufficient awareness about the disease is probably a major factor in its misdiagnosis, with undesirable morbidity and financial consequences. Chronic changes in the lung would lead to fibrosis and cor pulmonale. In some patients, pulmonary bleeding can be severe and fatal.

References

1. HEINER DC, SEARS JW. Chronic respiratory disease associated with multiple circulating precipitins to cow's milk. *Am J Dis Child* 1960; 100: 500–2.
2. BOAT TF, POLMAR SH, WHITMAN V, et al. Hyperactivity to cow milk in young children with pulmonary hemosiderosis and cor pulmonale secondary to nasopharyngeal obstruction. *J Pediatr* 1975; 87: 23–9.
3. LEE SK, KNIKER WT, COOK CD, et al. Cow's milk induced pulmonary disease in children. In: BARNES LA, ed. *Advances in Pediatrics*. Chicago, USA: 25, Year Book Medical Publishers 1978: 39–57.
4. FOSSATI G, PERRI M, CAREDDU G, et al. Pulmonary hemosiderosis induced by cow's milk proteins: a discussion of a clinical case. *Pediatr Med Chir* 1992; 14: 203–7.
5. OUCHTERLONY O. Diffusion in gel methods for immunological analysis. *Prog Allergy* 1962; 6: 30–154.
6. BAHNA SL, HEINER DC. *Allergies to Milk*. New York, USA: Grune & Stratton 1980.

7. BAHNA SL. Pathogenesis of milk hypersensitivity. *Immunol Today* 1985; 6: 153–4.
8. STAFFORD HA, POLMAR SH, BOAT TF. Immunologic studies in cow's milk-induced pulmonary hemosiderosis. *Pediatr Res* 1977; 11: 898–903.
9. HOLLAND NH, HONG R, DAVIS NC, et al. Significance of precipitating antibodies to milk proteins in the serum of infants and children. *J Pediatr* 1962; 61: 181–95.
10. PETERSON RD, GOOD RA. Antibodies to cow's milk proteins: their presence and significance. *Pediatrics* 1963; 31: 209–21.
11. TORRES JM, GIRON MD, CORZO JL, et al. Release of inflammatory mediators after cow's milk intake in a newborn with idiopathic pulmonary hemosiderosis. *J Allergy Clin Immunol* 1996; 98: 1120–3.
12. GJESING B, LOWENSTEIN H. Immunochemistry of food antigens. *Ann Allergy* 1984; 53: 602–8.
13. EULER AR, BYRNE WJ, AMENT ME, et al. Recurrent pulmonary disease in children: a complication of gastrointestinal reflux. *Pediatrics* 1979; 63: 47–51.
14. KJELLMAN B, ELINDER G, GARWICZ S, et al. Idiopathic pulmonary hemosiderosis in Swedish children. *Acta Paediatr Scand* 1984; 73: 584–8.
15. OHGA S, TAKAHASHI K, MIYAZAKI S, et al. Idiopathic pulmonary hemosiderosis in Japan: 39 possible cases from a survey questionnaire. *Eur J Pediatr* 1995; 154: 994–8.
16. YAO TC, HUNG IJ, WONG KS, et al. Idiopathic pulmonary haemosiderosis: an oriental experience. *J Paediatr Child Health* 2003; 39: 27–30.
17. HEINER DC. Pulmonary haemosiderosis. In: CHERNICK V, KENDIG EL Jr, eds. *Disorders of the Respiratory Tract in Children*. Philadelphia, USA: WB Saunders 1990: 498–509.
18. CHAINCHE LL, BOURGEOIS ML, FAUROUX B, et al. Long-term outcome of idiopathic pulmonary hemosiderosis in children. *Medicine (Baltimore)* 2000; 79: 318–26.
19. BAILEY P, GRODEN BM. Idiopathic pulmonary haemosiderosis: report of two cases and review of the literature. *Postgrad Med* 1979; 55: 266–72.
20. CASSIMOS CD, CHRYSSANTHOPOULOS C, PANAGIOTIDOU C. Epidemiologic observations in idiopathic pulmonary haemosiderosis. *J Pediatr* 1983; 102: 698–702.
21. SAEED MM, WOO MS, MACLAUGHLIN EF, et al. Prognosis in pediatric idiopathic pulmonary hemosiderosis. *Chest* 1999; 116: 721–5.
22. SOERGEL KH, SOMMERS SC. Idiopathic pulmonary haemosiderosis and related syndromes. *Am J Med* 1962; 32: 499–511.
23. COLOMBO JL, STOLZ SM. Treatment of life-threatening primary pulmonary hemosiderosis with cyclophosphamide. *Chest* 1992; 102: 959–60.