Heiner Syndrome Mimicking an Immune Deficiency
Jerome A. Sigua, MD; Michael Zacharisen, MD

ABSTRACT
Heiner syndrome is a rare but reversible non-IgE mediated hypersensitivity to cow’s milk resulting in an atypical pulmonary disease in infants and young children. There is often a delay in diagnosis in this disorder due to its unusual presentation with heterogeneous manifestations. Such infants usually have chronic or recurrent upper or lower respiratory tract symptoms, suggestive of recurring infections such as otitis media or pneumonia. The patchy infiltrates on chest x-ray are commonly mistaken for pneumonia, yet are refractory to antibiotic treatment. Systemic features such as fever, vomiting, diarrhea, and failure to thrive further contribute to the difficulty in making a prompt diagnosis. Only a few case reports have been published. We report a case of this unique milk-induced pulmonary syndrome in a hospitalized 12-month-old child, which illustrates the importance of considering this diagnosis in any child with unexplained lung infiltrates.

CASE PRESENTATION
A 12-month-old Hmong boy, born full term without complications in Wisconsin with a normal newborn screen, was hospitalized in a tertiary medical center with a suspected multifocal pneumonia that was refractory to outpatient antibiotic treatment. He had a 2-month history of persistent cough with occasional sputum production, dyspnea without wheeze, progressive anorexia, and intermittent fevers. He did not have vomiting or diarrhea but had lost approximately 3 pounds.

His past medical history was otherwise unremarkable; he had normal growth and development and was reaching appropriate developmental milestones. There was no family history of known immune deficiencies or autoimmune disorders. There was no pet or animal exposure, nor travel outside of his immediate home.

A chest x-ray (CXR) from 2 months prior when his symptoms began was remarkable for a right upper lobe infiltrate (Figure 1A). At that time, he had a concurrent right otitis media and was treated as an outpatient with amoxicillin for a projected 10-day course. His cough worsened before he completed this antibiotic, therefore his treatment was changed to cefdinir for a projected 10-day course. His cough did not abate after completing this course. A repeat CXR showed a persistent yet improved right upper lobe infiltrate (Figure 1B), therefore his antibiotic treatment was extended with a course of azithromycin for 5 days. One week later a repeat CXR appeared largely unchanged. He was treated with amoxicillin/clavulanate for an additional 10 days. His symptoms improved mildly, though incompletely, so his treatment with amoxicillin/clavulanate was extended for an additional 20 days. Despite adherence to this regimen, he continued to cough with occasional post-tussive nonbloody emesis. He had no nasal discharge, wheeze, or hemoptysis. His oral intake gradually diminished. He developed intermittent fevers to 101°F-102°F twice weekly. He did not have rash, reflux, vomiting, changes in his bowel habits, or blood in his stools.

On arrival to the emergency department, he was febrile with a temperature of 101.5°F and hypoxemic with an oxygen saturation of 88% on room air. Physical examination was unrevealing other than mild rhonchi noted in his right upper and left lower lung fields. CXR showed an increased right upper lobe consolidation with left basilar and retrocardiac air space opacities that were significantly worse compared to his previous CXR (Figure 1C). Laboratory studies revealed a leukocytosis with mild eosinophilia (white blood cell [WBC] 13.6 K/uL, absolute eosinophil count 816 K/uL), a profound microcytic anemia (hemoglobin 7.1 g/dL, MCV 52 fl), and a mild thrombocytosis (platelets 582,000 K/uL). Iron studies were consistent with iron deficiency anemia (low iron 17 ug/dL, elevated total iron-binding capacity [TIBC]).
554 ug/dL, low ferritin 7.9 ng/mL). Inflammatory markers were mildly elevated (erythrocyte sedimentation rate [ESR] 13 mm/hr, C-reactive protein [CRP] 1.1 mg/dL). Blood cultures were without growth.

Due to concern for an atypical or fungal pneumonia, pulmonary hemorrhage, or pulmonary hemosiderosis, a bronchoscopy was performed, which on gross inspection appeared normal other than mild edema and erythema of his bronchi and bronchioles. Bronchoalveolar lavage (BAL) cytology revealed 1600 red blood cells and 1600 nucleated cells of predominant neutrophils and few foamy macrophages. There were no iron-laden macrophages seen. Bacterial and fungal cultures, mycoplasma PCR, viral studies, and acid-fast bacilli smear of the BAL were negative. Additionally, blastomyces and histoplasma serologies were negative. He was continued on treatment with amoxicillin/clavulanate, with clindamycin added for additional microbial coverage; however, his clinical status remained unchanged.

Recurrent aspiration essentially was excluded by a normal swallow evaluation. Because an infectious cause could not be determined, a vasculitis or autoimmune disorder was considered. An anti-nuclear antibody (ANA) test was positive at a titer of 1:640 with a speckled pattern. More specific tests including anti-double-stranded DNA (anti-DS DNA) for systemic lupus erythematosus and anti-glomerular basement membrane (anti-GBM) antibodies for Goodpasture’s Syndrome were negative.

An immunology consultation was requested by the primary team for concern of an immunodeficiency. Further history obtained by the consulting service indicated that cow’s milk formula at birth elicited nonbloody diarrhea, therefore prompting a switch to a soy-based formula that was better tolerated. At age 10 months, cow’s milk formula was reintroduced. Within 1 week of this transition, his chronic cough, dyspnea, intermittent fevers, and progressive anorexia had started.

With this additional history, there was a high index of suspicion for a milk-induced pulmonary syndrome known as Heiner syndrome (HS), especially given the precise correlation of cow’s milk reintroduction with subsequent symptom onset. First, a basic screen of his immune function was undertaken. He demonstrated normal tetanus antibody titers of 1.487 IU/mL (>0.150 IU/mL), elevated IgG 1739 mg/dL (174-857 mg/dL), normal IgA 56 mg/dL (10-75 mg/dL), and slightly elevated IgM 107 mg/dL (22-95 mg/dL). A serum specific IgE to cow’s milk was negative. Serum precipitating IgG antibodies to all 9 cow’s milk protein fractions tested were strongly positive.

Even prior to return of the milk precipitin assay results, a cow’s milk-free diet was initiated due to a strong suspicion of HS. Within 1 to 2 days, he exhibited full recovery from his cough, dyspnea, fever, and anorexia. He was discharged home shortly thereafter on a strict soy-based diet. Two months later, a repeat CXR showed complete resolution of the previously identified
pulmonary opacities and infiltrates (Figure 1D). Collectively, all of these findings were strongly suggestive of HS.

DISCUSSION

In 1962, Heiner first reported the presence of precipitating antibodies to several cow’s milk antigens in the sera of 7 infants who had presented with varied manifestations including chronic cough, lung infiltrates, diarrhea, failure to thrive, and anemia. Such patients improved after either transitioning to a diet with denatured milk or complete elimination of cow’s milk.¹

The precise mechanism responsible for this syndrome is still poorly understood. Whether or not the precipitating antibodies to milk are themselves causative of this disease is not known; however, a type III hypersensitivity or immune complex deposition reaction has been strongly suspected. Heiner and his colleagues had previously demonstrated the presence of IgG, C3, fibrin, and milk antigen deposition on immunofluorescence studies of lung tissue biopsies in a couple of infants.² Additionally, a cell-mediated reaction has also been postulated as contributing to the pathogenesis of this disease.³

Approximately 1% of healthy asymptomatic children are estimated to have precipitating IgG antibodies to milk,⁴ while 4% to 6% of children with chronic respiratory tract disease are thought to have these milk precipitins.⁵ Among those children with HS, approximately 10% are believed to have the severe form of the disease with pulmonary hemosiderosis. Although the onset of symptoms usually occurs before the age of 1 year, it has been reported to occur as late as age 5.²

HS is primarily a clinical diagnosis with no specific confirmatory test. Features of this disorder include upper or lower respiratory tract symptoms such as cough, rhinitis, dyspnea, or wheeze, gastrointestinal symptoms such as vomiting or diarrhea, failure to thrive, fever, CXRs with patchy and fleeting opacities or infiltrates, and varying degrees of peripheral eosinophilia or iron deficiency anemia. Although common, the presence of iron-laden macrophages on bronchial or gastric aspirates is not exhibited by all such children. A majority of children, however, will demonstrate the presence of precipitating IgG antibodies to cow’s milk.⁶ Some may even have evidence of serum specific IgE to cow’s milk.¹ Rarely, hepatomegaly, splenomegaly, or nonspecific lymphadenopathy can be seen.⁷ What ultimately unifies and supports the diagnosis of HS is resolution of all of the above findings after strict cow’s milk avoidance, which our patient exhibited.

Recovery after elimination of cow’s milk is usually immediate, with a typical time range of 5 to 21 days.³ It is not clear how long one should avoid cow’s milk, since it has been reported that subsequent early reintroduction or challenge with cow’s milk can lead to recurrence of symptoms.⁶ In general, it is believed that most can tolerate cow’s milk within a few years. Prior to reintroduction, some children are able to tolerate denatured or heated milk.⁴

If left undiagnosed and untreated, delayed manifestations of alveolar hypoventilation, pulmonary hypertension, or cor pulmonale can occur.³ Death from massive acute pulmonary hemorrhage was reported in a 5-year-old boy with suspected HS.⁷

CONCLUSION

Our case illustrates how Heiner syndrome, often overlooked, can resemble an infection or immune deficiency, contributing to its misdiagnosis, delayed intervention, and increased medical expenses. Interestingly, our patient’s elevated ANA may represent a novel finding that has not been previously reported. While it is essential to perform a basic immune evaluation in individuals presenting with recurrent, severe or unusual infections, HS in particular should be considered in the differential diagnosis in any child with unexplained pulmonary infiltrates to avoid harmful consequences.

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