Crescentic glomerulonephritis in a child with Heiner syndrome

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Heiner syndrome is a food-induced pulmonary hypersensitivity disease that predominantly affects infants. Chronic respiratory symptoms with pulmonary infiltrates on radiography, positive milk precipitins and resolution of findings upon removal of cow's milk constitute the main features. Severe cases may present with pulmonary hemosiderosis. Few renal manifestations associated with this syndrome have been reported so far. Here we report the first case of Heiner syndrome complicated by crescentic glomerulonephritis after 5 years of follow-up.

Key words: crescentic glomerulonephritis, pulmonary hemorrhage, milk allergy, Heiner syndrome.

Crescentic glomerulonephritis (GN), also known as rapidly progressive glomerulonephritis (RPGN), is relatively rare in children. Rapid loss of renal function and morphologically extensive crescents (>50%) are characteristic. It can be as immune complex-mediated, anti-glomerular basement membrane (anti-GBM) antibody-mediated and pauci-immune glomerulonephritis[1].

Heiner syndrome is a milk-induced pulmonary disease first described in seven infants by Heiner et al. in 1962[2]. The most common manifestations are chronic respiratory symptoms, failure to thrive, iron deficiency anemia, eosinophilia, precipitating antibodies to milk proteins, patchy or peribronchial infiltrates, localized atelectasis on chest roentgenograms, pulmonary hemosiderosis and resolution on a cow's milk-free diet[3]. However, few renal manifestations associated with this syndrome have been reported in the available literature[4,5]. Here we report a case of Heiner syndrome associated with crescentic GN.

Case Report

A 3-year-old boy was referred to our emergency service with respiratory distress and hemoptysis. He was immediately intubated and taken to the intensive care unit. His past medical history was remarkable for recurrent bronchitis. On physical examination, his height and weight parameters were below the 3rd centile. He had tachypnea and tachycardia with pallor. Laboratory results were remarkable for hypochromic microcytic anemia, eosinophilia and iron deficiency. Coagulation tests, hemolysis parameters, blood chemistry and urine analyses were normal. The erythrocyte sedimentation rate and C-reactive protein levels were increased. Tests for antinuclear antibodies (ANA), anti-double-stranded DNA (anti-DNA) antibodies, perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies (p/c-ANCA) and antiglomerular basal membrane (anti-GBM) antibodies were negative, and complement levels (C_3, C_4) were normal. Available microbial tests, metabolic screenings and a sweat test were negative. Levels of serum immunoglobulin (Ig) other than IgE were within normal limits (Table I). Specific IgE and skin prick testing for milk and wheat were positive. A chest-X ray demonstrated reticulonodular opacities; computed tomography showed diffuse ground-glass opacities in the lungs. Pneumonia was not ruled out, and empiric antibiotic treatment was initiated. No hemorrhagic focus was existent on bronchoscopy. Hemosiderin-laden macrophages were seen in the bronchoalveolar lavage (BAL) fluid. Echocardiography and pulmonary angiography were normal. An

initial diagnosis of Heiner syndrome was made due to findings consisting of recurrent respiratory symptoms, failure to thrive, iron deficiency anemia, eosinophilia, hypersensitivity to cow's milk and pulmonary hemosiderosis. A low dose of prednisolone and azathioprine were prescribed. Shortly after this, pulmonary hemorrhage disappeared. Milk and wheat were eliminated from the diet. The pulmonary infiltrates cleared within days. The diagnosis was confirmed with positive milk challenge tests. He was discharged with low-dose prednisolone and azothioprine.

During the next five years, the patient failed to receive the prescribed medications and was frequently hospitalized with recurrent hemoptysis attacks, which typically occurred after neglecting to follow the diet. Milk and wheat elimination rapidly resolved his clinical and radiological findings during each stay.

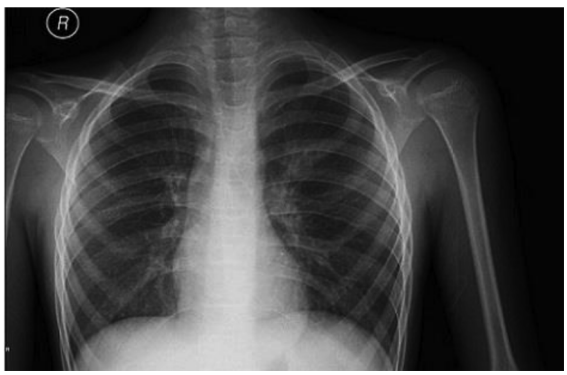

Fig. 1. Posteroanterior chest radiograph demonstrating bilateral paracardiac infiltrates.

He rarely had gastrointestinal symptoms such as nausea and diarrhea. During the last hemoptysis attack, he presented with edema, macroscopic hematuria and hypertension. Laboratory investigation showed heavy proteinuria, anemia, azotemia, hypoalbuminemia and hypocomplementemia. The tuberculin skin test and available microbial tests were negative. The antistreptolysin O (ASO) titer was normal. ANA, anti-DNA, p/c-ANCA and anti-GBM tests were negative (Table 1). Chest graphy demonstrated bilateral paracardiac infiltrates (Fig. 1). Renal biopsy was performed. Light microscopy showed diffuse crescents affecting nearly half of the glomeruli (Fig. 2a). Immunofluorescence (IF) studies revealed the peripheral granular deposition of C_3 and C_1q along the glomeruli, mesengeal deposition of IgG and tubular segmental deposition of IgA, IgM and C_4 along the distal tubules (Fig. 2b). Crescentic glomerulonephritis was diagnosed on the basis of histopathological findings. The treatment was revised, with a combination of cyclophosphamide and prednisolone. The proteinuria and hematuria disappeared, and serum complements reached normal levels within four weeks of the new therapy. After two years of follow-up, the patient's lupus serology was still negative, and C_3, C_4, renal functions and urinary protein excretion were within normal ranges. He still suffers from hemoptysis attacks whenever he neglects to follow the diet.

Discussion

Our patient mimicked a clinical picture of

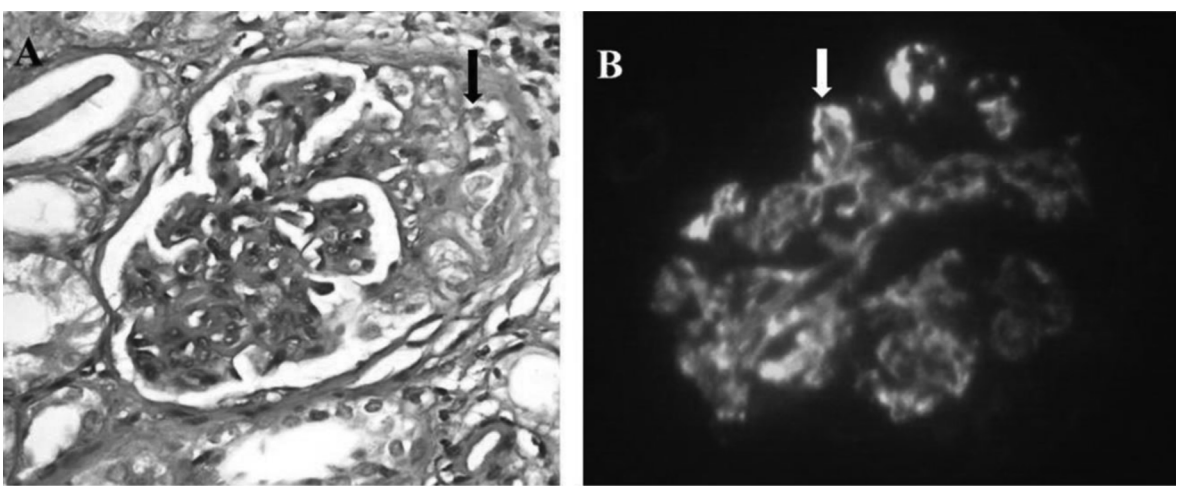

Fig. 2. A. The light microscopic examination shows the crescent affecting nearly half of the glomeruli (black arrow) (H&E, X400). **B.** Immunofluorescence microscopy demonstrates diffuse granular deposition of immunoglobulin G (white arrow) in the glomerular capillary basement membranes.

pulmonary renal syndrome (PRS) with diffuse alveolar hemorrhage and crescentic GN. So, we examined the probable causes of PRS, including systemic lupus erythematous (SLE), Wegener's granulamatosis (WG), anti-GBM disease, Henoch-Schönlein purpura (HSP), IgA nephropathy, Churg-Strauss syndrome (CSS) and infection- or drug-induced GN[6].

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multisystem involvement. Pulmonary hemorrhage usually follows renal disease in SLE; however, it may be an initial manifestation[7]. Despite hypocomplementemia and full-house pattern on IF, our patient was regarded as unlikely to have SLE because of the absence of additional systemic involvement, and negative serology for ANA and anti-DNA. Wegener's granulamatosis is characterized by necrotizing and granulomatous inflammation of the respiratory tracts, systemic vasculitis and GN. The vast majority of cases are ANCA related[6]. However, WG seemed to be very unlikely in our patient, since we could not document recurrent sinusitis, necrotizing vasculitis or ANCA positivity. Autoantibodies against type IV collagen in glomerular and alveolar basement membranes induce pulmonary hemorrhage and GN in anti-GBM disease. Linear deposition of IgG along the GBM is characteristic[8]. However, hypocomplementemia, IF pattern and negative anti-GBM were incompatible with anti-GBM disease in our patient.

Churg-Strauss syndrome is a small- and medium-vessel vasculitis. Asthma, allergic rhinitis and sinusitis are common. ANCA

Table I. Patient's Laboratory Data During the First and Last Hemoptysis Episodes

Parameter	First episode	Last episode	Reference range
Hb (g/dl)	3.1	7.1	11.2-13.5
WBC (10^3/ml)	7.4	12	5.5-15.5
Plt (10^3/ml)	669	554	150-400
PT/aPTT (/sec)	12/24	11/21	10-14/20-35
BUN/Scr (mg/dl)	16/0.4	44/1.9	5-18/0.2-0.7
Albumin (g/dl)	3.6	2.1	3.5-5.4
Fe/Ferritin (mg/dl)	10/<7	15/10	20-124/7-140
ESR (/h)	40	20	0-15
CRP (mg/L)	10	5	0-5
ASO (IU/ml)	110	125	0-200
C_3/C_4 (mg/dl)	135/39	20/8.6	65-165/16-160
ANA/Anti-DNA	(-)/(-)	(-)/(-)	(-)
p/c-ANCA	(-)/(-)	(-)/(-)	(-)
Anti-GBM	(-)	(-)	(-)
IgG (mg/dl)	797	836	345-1236
IgM (mg/dl)	200	164	43-207
IgA (mg/dl)	55	60	14-159
IgE (IU/ml)	1431	1280	0-230
Urine protein	(-)	(++++)	(-)

Hb: hemoglobin, WBC: white blood cell, plt: platelet, PT: prothrombin time, aPTT: activated partial thromboplastin time, BUN: blood urea nitrogen, Scr: serum creatinine, Fe: iron, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ASO: antistreptolysin O, C3: complement 3, C4: complement 4, ANA: anti nuclear antibody, anti-DNA: anti-double-stranded DNA, p/c-ANCA: perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibody, anti-GBM: anti-glomerular basal membrane antibody, Ig: immunoglobulin

presents in about 40-60% of cases[9]. The main renal histopathological pattern is pauci-immune necrotizing crescentic GN[10]. Despite the clinical resemblance, negative ANCA, hypocomplementemia and immune deposits on IF were incompatible with CSS. Neither did the patient have the purpura, abdominal pain or joint symptoms suggesting HSP. There was no history of recurrent hematuria and IgA deposition was not prominent, as seen in IgA nephropathy. Finally, there was no evidence of recent infection or drug usage that might lead to GN.

We believe that Heiner syndrome is likely to be the most probable diagnosis for the pulmonary features and food hypersensitivity described in this case. The dramatic clinical and radiological improvements after elimination of milk support our opinion. Chronic aspiration, bronchial asthma, cystic fibrosis (CF), hypersensitivity pneumonitis and bronchopulmonary aspergillosis were considered in the differential diagnosis. However, there was no history of recurrent aspiration, and the typical diet-induced pulmonary hemorrhage attacks could not be explained by simple bronchial asthma. The normal salt level on the sweat test was not compatible with CF. The lack of chronic inhalant exposure and lypmhocytosis on BAL examination kept us from fixing on hypersensitivity pneumonitis. Bronchopulmonary aspergillosis was thought to be unlikely in our patient, as he did not have skin reactivity to *Aspergillus* antigens or precipitating serum antibodies to *A. fumigatus*.

The literature concerning Heiner syndrome is limited to a few reports, and the underlying immunologic mechanism remains unclear. Immune complexes and/or autoantibodies have been thought to play a role[3]. On the other hand, the full-house IF pattern on renal biopsy, low C_3-C_4 and lack of evidence of a major cause of RPGN suggested to us an idiopathic immune complex nephritis. Therefore, PRS in our patient could be explained as the coincidence of Heiner syndrome and idiopathic immune complex nephritis. Similarly, van der Ent et al[4]. reported two children with a syndrome of pulmonary hemorrhage and immune complex nephritis. Necrotizing glomerulonephritis with granular immune deposits along the GBM was demonstrated. The authors suggested that pulmonary lesions precede renal abnormalities, and that immune complex glomerulonephritis is an unusual complication of idiopathic pulmonary hemosiderosis[4]. In the present case, it could be postulated that milk antigens might have triggered an immune complex reaction resulting in pulmonary and renal abnormalities.

In conclusion, physicians might consider Heiner syndrome in children with unexplained chronic pulmonary symptoms, iron deficiency and a proven milk allergy. The overlapping glomerulonephritis in this Heiner case suggested that milk allergy might have led to an extrapulmonary disorder via an immune complex reaction.

REFERENCES

1. Bagga A, Menon S. Rapidly progressive glomerulonephritis. In: Geary DF, Schaefer F (eds). Comprehensive Pediatric Nephrology. Philadelphia: Mosby; 2008: 319-327.
2. Heiner DC, Sears JW, Kniker WT. Multiple precipitins to cow's milk in chronic respiratory disease. A syndrome including poor growth, gastrointestinal symptoms, evidence of allergy, iron deficiency anemia and pulmonary hemosiderosis. Am J Dis Child 1962; 103: 634-654.
3. Moissidis I, Chaidaroon D, Vichyanond P, Bahna SL. Milk-induced pulmonary disease in infants (Heiner syndrome). Pediatr Allergy Immunol 2005; 16: 545-552.
4. Van der Ent CK, Walenkamp MJ, Donckerwolcke RA, van der Laag J, van Diemen-Steenvoorde R. Pulmonary hemosiderosis and immune complex glomerulonephritis. Clin Nephrol 1995; 43: 339-341.
5. Fossati G, Perri M, Careddu G, Mirra N, Carnelli V. [Pulmonary hemosiderosis induced by cow's milk proteins: a discussion of a clinical case]. [Article in Italian] Pediatr Med Chir 1992; 14: 203-207.
6. Papiris SA, Manali DE, Kalomenidis I, Kapotsis GE, Karakatsani A, Roussos C. Bench-to-bedside review: pulmonary-renal-syndromes—an update for the intensivist. Critical Care 2007; 11: 213.
7. Pego-Reigosa JM, Medeiros DA, Isenberg DA. Respiratory manifestations of systemic lupus erythematosus: old and new concepts. Best Pract Res Clin Rheumatol 2009; 23: 469-480.
8. Williamson SR, Phillips CL, Andreoli SP, Nailescu C. A 25-year experience with pediatric anti-glomerular basement membrane disease. Pediatr Nephrol 2011; 26: 85-91.
9. Twilt M, Benseler S, Cabral D. Granulomatosis with polyangiitis in childhood. Curr Rheumatol Rep 2012; 14: 107-115.
10. Sinico RA, Di Toma L, Maggiore U, et al. Renal involvement in Churg-Strauss syndrome. Am J Kidney Dis 2006; 47: 770-779.