Treatment of Life-threatening Primary Pulmonary Hemosiderosis with Cyclophosphamide

John L. Colombo, M.D., F.C.C.P.; and Steven M. Stolz, M.D.†

This report describes a five-year-old boy with severe pulmonary hemorrhage caused by primary pulmonary hemosiderosis with cow’s milk sensitivity. After failing to respond to corticosteroids and azathioprine, he dramatically improved after being given cyclophosphamide. He worsened after discontinuation of cyclophosphamide on two occasions and improved significantly with its reinstitution. Cyclophosphamide was continued for 14 months without further bleeding or adverse effects. The patient has remained in remission for nearly five years. Cyclophosphamide may be a life-saving alternative therapy for refractory pulmonary hemorrhage with pulmonary hemosiderosis.

(CHEST 1992; 102:959-60)

Most cases of primary pulmonary hemosiderosis occur in children and young adults. Although the etiology is unknown, a significant number of children with this disorder appear to have pulmonary bleeding related to milk ingestion and they demonstrate high titers of serum precipitins to cow’s milk (Heiner’s syndrome). Standard treatment is milk elimination diet and corticosteroids, if symptoms warrant.1 We report a patient with Heiner’s syndrome who developed massive pulmonary hemorrhage while taking daily steroid therapy and adhering to a milk-free diet. Cyclophosphamide was started on three separate occasions with worsening of bleeding after each discontinuation and rapid improvement after each institution of therapy. We believe this is the first report of such treatment in the English-language literature.

CASE REPORT

The patient was a five-year-old black boy who was admitted to the hospital with acute respiratory distress and hemoptysis. At two years of age this patient was diagnosed with Heiner’s syndrome based on clinical findings, patchy infiltrates on a chest radiograph, sighting of hemosiderin-laden macrophages in gastric aspirate, a positive serum radioallergosorbent test for milk and histologic findings of an open-lung biopsy. Quantitative immunoglobulin levels were normal to elevated with IgG being 1,335 mg/dl; IgA, 244 mg/dl; and IgM, 135 mg/dl. At that time, prednisone therapy of 10 mg twice daily and a milk-free diet were begun.

The patient remained asymptomatic for more than two years with the aforementioned therapy. The parents denied any intake of milk products. One week prior to admission he developed a cough and mild dyspnea. On the morning of admission he was taken to a community hospital with rapidly progressive respiratory distress. Tracheal intubation revealed a copious return of fresh blood.

*From the Section of Pulmonology, Department of Pediatrics, University of Nebraska Medical Center, Omaha.
†Presently Chief, Pediatric and Allergy Services, Air University Regional Hospital, Montgomery, Ala.
Reprint requests: Dr. Colombo, Department of Pediatrics, University of Nebraska Medical Center, 600 South 42nd Street, Omaha 68198-8190

Physical examination demonstrated respiratory distress and minimal responsiveness. Blood pressure was 110/59 mm Hg; pulse, 141 beats per minute; rectal temperature, 37.8°C; respiratory rate, 76 breaths per minute with a ventilator rate of 40 breaths per minute. A chest radiograph showed bilateral severe diffuse infiltrates with air bronchograms. The hemoglobin concentration was 81 g/L. Serum antibodies were positive for specific IgE and IgG 4 to alphalactalbumin, casein and milk. Disseminated intravascular coagulation screens and complement activity were normal.

Intravenously administered hydrocortisone, antibiotics and fluids were instituted. Tracheal secretions continued to be bloody throughout the first hospital day. Urine, after catheter placement, was dark red with initial urinalysis showing 2 to 7 red blood cells per HPF and 4 to 8 hemoglobin cases per LPF. Flexible bronchoscopy demonstrated coating of main stem bronchi with fresh blood without any localized source. Because of the intrapulmonary hemorrhage and hematuria, percutaneous renal biopsy was performed to evaluate for Goodpasture’s syndrome. The patient’s clinical status rapidly deteriorated with significantly increased oxygen requirements. One intravenous dose of cyclophosphamide, 1.5 mg/kg, was given. Renal biopsy revealed no abnormalities and serum antiglomerular basement membrane antibody was negative. With Goodpasture’s syndrome excluded, cyclophosphamide was discontinued. The day following cyclophosphamide administration there was marked diminution of blood return from the endotracheal tube. Within 72 h, increasing endotracheal blood was suctioned and arterial blood gas values deteriorated (Fig 1). At that time, intravenously administered azathioprine, 1 mg/kg daily, was begun. The patient continued to deteriorate through the morning of day 7, at which time intravenously administered cyclophosphamide (1.5 mg/kg/day) was resumed. During the next 24 to 48 h clinical status and gas exchange improved (Fig 1). Extubation was accomplished on day 14. On day 17, cyclophosphamide was discontinued, azathioprine and hydrocortisone were continued. The patient remained stable with a hemoglobin value of 137 g/L. He was discharged on day 22 with oxygen saturation values between 92 and 99 percent while breathing room air. Discharge medications included daily doses of prednisone, 1.5 mg/kg, and azathioprine, 2.5 mg/kg.

Twenty-four hours following discharge, the patient developed acute dyspnea. Arterial blood gas values while breathing room air were pH, 7.40; Pco₂, 35 mm Hg; and Po₂, 40 mm Hg. The hemoglobin concentration was 128 g/L. A chest radiograph showed progression of diffuse infiltrates. The patient continued to deteriorate with the respiratory rate increasing to the 70s and worsening of chest radiograph infiltrates. The hemoglobin concentration fell to 89 g/L. Mechanical ventilation was instituted. There was a large return of fresh blood from the endotracheal tube. Intravenous cyclophosphamide was resumed. Improvement was again noted.

**Figure 1**. Changes in P(A-a)O₂ in relationship to cyclophosphamide therapy. Each box indicates a single dose of cyclophosphamide. Arterial oxygen measurements are plotted every 4 h.
during the following 24 to 48 h with total clearing of endotracheal tube blood in three days. On the fifth day, extubation was accomplished. The patient was discharged on a regimen of prednisone, 1.5 mg/kg daily, and orally administered cyclophosphamide, 2.5 mg/kg three times weekly. Cyclophosphamide therapy was continued for 14 months and alternate-day dosage of prednisone was given for 26 months. Chemoprophylaxis with cotrimoxazole was used during the prednisone therapy. He also remained on a milk-free diet. The disease has remained in remission without further medications for approximately five years.

**DISCUSSION**

The etiology of primary pulmonary hemosiderosis remains unknown. An immunologic basis is supported by observations of improvement in some patients receiving immunosuppressive therapy. Improvement in acute symptomatology following administration of corticosteroids was reported by Browning and Houghton in 1956, although an epidemiologic survey of 30 children with this disease concluded that corticosteroid therapy did not alter the long-term course or prognosis. Other reports have suggested that addition of azathioprine appeared to produce remission after corticosteroids failed to do so.

To our knowledge, the only reported cases of primary pulmonary hemosiderosis treated with cyclophosphamide are found in the European literature. Apparent cyclophosphamide-induced remission of primary pulmonary hemosiderosis was reported in a 4-year-old girl and a 13-year-old boy after corticosteroid therapy failed. Others have reported improvement of acute symptoms with a combination of prednisone and cyclophosphamide therapy. O'Donohue reported a patient with the original diagnosis of primary pulmonary hemosiderosis, but with many features suggestive of Wegener's granulomatosis, showing remission on two occasions with cyclophosphamide therapy.

As documented by clinical status and P(A-a)O₂ values, our patient worsened during azathioprine and corticosteroid therapy but promptly improved after a single dose of cyclophosphamide. This scenario occurred two additional times with the patient's condition changed from one of severe ventilatory failure requiring 100 percent oxygen and high ventilator pressures to rapid discontinuation of mechanical ventilation after resumption of cyclophosphamide therapy. Improvement was noted on all three occasions within 24 to 48 h of cyclophosphamide treatment and remission has been maintained for nearly five years. While primary pulmonary hemosiderosis has a remitting nature, the timing of clinical improvement in this case strongly suggests a beneficial response to cyclophosphamide.

The finding of autoimmune hemolysis associated with primary pulmonary hemosiderosis has been reported. This patient's hemoglobinuria rapidly improved and was attributed to this etiology.

Cyclophosphamide possesses potent antiinflammatory and immunosuppressive actions. It inhibits both humoral and cell-mediated reactions through unknown mechanisms. Possible side effects include leukopenia, thrombocytopenia, hemorrhagic cystitis, interstitial pulmonary fibrosis, sterility and secondary malignancy.

We propose that this child's response to cyclophosphamide was due to the drug's antiinflammatory and immunosuppressive properties. Its use appeared to be life-saving in this patient and without adverse effects, although the bearing on the long-term outcome is less clear. We report this case for its potential value to English-speaking physicians. Due to the frequency and severity of side effects associated with cyclophosphamide, we believe that its use should be limited to life-threatening exacerbations of primary pulmonary hemosiderosis which have not responded to traditional therapy.

**REFERENCES**


**Implantable Cardioverter Defibrillator Infection Causing Constrictive Pericarditis**

Arnold H. Kassanoff, M.D.; Charles B. Levin, M.D.; Christopher R. C. Wyndham, M.D.; and Laurence J. Mills, M.D.

*From the Department of Medicine, Presbyterian Hospital of Dallas.
Reprint requests: Dr. Kassanoff, 7150 Greenville, Dallas 75231*