

Pneumocystis carinii Pneumonia in an Infant with the Hyperimmunoglobulinemia E Syndrome*

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ABSTRACT

A 4-month-old female presented with "cold" groin abscesses, otitis, and interstitial pneumonia. Open lung biopsy showed extensive *Pneumocystis carinii* pneumonitis. An immunologic workup revealed exaggerated blood levels of immunoglobulin E (over 2000 IU/ml by 10 months of age) and abnormal polymorphonuclear chemotaxis, both characteristic of the hyperimmunoglobulinemia E (HIE) syndrome. No well-defined lymphocytic defect known to predispose to opportunistic infection was discovered in this patient. We believe that our patient represents the first reported association of *P. carinii* pneumonia in a patient with HIE syndrome. This finding has implications for the spectrum of immunologic aberrations that may predispose to *P. carinii* pneumonia and also should raise consideration for *P. carinii* as a potential etiologic agent of pneumonitis in patients with HIE syndrome.

INTRODUCTION

IN 1972, Buckley, Wray, and Belmaker⁽¹⁾ described two adolescent boys who had recurrent pyogenic infections and extreme hyperimmunoglobulinemia E (HIE). The HIE syndrome has been recognized subsequently in both genders and among numerous racial groups.⁽¹⁻⁶⁾ The syndrome is characterized by markedly elevated levels of circulating immunoglobulin E (IgE) and recurrent serious infections, most commonly staphylococcal or candidal.^(4,6) The cause of the defect and the basis of the recurrent infections are not understood, and abnormal neutrophil

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chemotaxis, which has often been associated with the HIE syndrome, has not been a constant feature.⁽³⁻⁶⁾ The exaggerated IgE levels are thought to result from deficient suppressor T-cell activity in inhibiting IgE production.⁽⁶⁾

Several other immunologic abnormalities have been reported to occur in patients with HIE syndrome, including decreased numbers of circulating suppressor T lymphocytes^(7,8) and depressed mitogenic responses to candida and tetanus antigens.^(1-3,5) However, none of these abnormalities have been consistent findings in the HIE syndrome.^(6,9) Opportunistic infections in HIE syndrome patients have consisted predominantly of mucocutaneous candidiasis, although cryptococcosis of the colon and esophagus and ileocecal histoplasmosis have been reported.⁽¹⁰⁻¹²⁾

To our knowledge, there have been no previous reports of infection by *Pneumocystis carinii* in these patients, and this paper describes a child with clinical and laboratory features typical of HIE syndrome who developed severe pneumonia due to this organism.

CASE REPORT

Our patient was a 4-month-old white female admitted to Columbus Children's Hospital for tachypnea and groin swelling. The parents had noticed increasing tachypnea and cough over the preceding 6 weeks. The week before hospitalization she was noted to have cyanosis during crying and coughing, and she developed small pustular lesions on the scalp and in the inguinal areas. She was given erythromycin ethylsuccinate, and the pustular lesions disappeared. Three days before admission she developed swelling in both groins which continued to increase, despite erythromycin therapy, and cefaclor was begun. She had remained afebrile until the night before admission when she developed a low-grade fever.

This patient had been a full-term newborn whose neonatal course was complicated by hyperbilirubinemia (peak 19 mg/dL at 4 days of age), which resolved after phototherapy. At 2 months of age she developed a fine pustular rash on the face that resolved with a 10-day course of erythromycin ethylsuccinate. One week later she was admitted to her local hospital with rhinorrhea, cough, tachypnea, and bilateral otitis media. Chest roentgenogram was normal. She was treated with intravenous antibiotics and discharged 2 days later on amoxicillin. She had been given two immunizations with DPT and OPV and had never received infusions of any blood product.

The patient's mother and 5-year-old brother were healthy, but the father reported recurrent skin abscesses beginning in early adulthood and remained asymptomatic while on chronic cefadroxil. Risk factors for AIDS acquisition were absent from both parents. Physical examination at admission showed a well-developed, well-nourished white female in moderate respiratory distress. Temperature was 102.6°F, respiratory rate 110, and pulse 158. She had bilateral otitis media, no adventitious lung sounds despite marked tachypnea, and multiple 0.5- to 5-cm fluctuant masses in both groins and the proximal, medial aspects of the thighs. There were mild ecchymotic changes over some of the lesions on the thighs but no erythema or warmth.

A complete blood count showed 20,300 leukocytes/mm³ with 23% neutrophils, 51% lymphocytes, and 20% eosinophils. Hemoglobin was 12.0 g/dl, and platelet count was 693,000/mm³. Arterial blood gas with an FIO₂ of 0.4 showed pO₂ 101, pCO₂ 28, pH 7.53. A chest roentgenogram showed a mild interstitial infiltrate and a normal-appearing thymus. An aspirate of one of the thigh lesions and Gram-stained smear showed many neutrophils and Gram-positive cocci in clusters. Tympanocentesis fluid revealed a few neutrophils and rare Gram-positive cocci.

Therapy was instituted including supplemental oxygen, intravenous fluids, and nafcillin, gentamicin, and trimethoprim/sulfamethoxazole (TMP/SMZ, 20 mg TMP/kg per day).

Bacterial cultures of tympanocentesis fluid and abscess aspirate grew *Staphylococcus aureus*. Cultures of blood, cerebrospinal fluid, and urine revealed no pathogens. Cytomegalovirus was recovered from urine, and poliovirus type I (presumed vaccine strain) grew from urine and stool. Respiratory secretions were culture negative for viruses, and smears for fungi, acid-fast orga-

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nisms, and *Legionella pneumophila* were negative. Serum for pneumocystis antigen (L. Pifer, Memphis, TN) was negative.

The patient's clinical respiratory status declined, and chest roentgenograms showed worsening of the interstitial infiltrate and new alveolar filling. On the third hospital day, open lung biopsy and incision and drainage of the large groin abscess were performed.

Sections of lung biopsy material showed interstitial pneumonitis with alveolar cell hyperplasia and pink granular intraalveolar exudate. Large numbers of cysts and trophozoites of *P. carinii* were identified (Fig. 1). No viral inclusions, bacteria, or fungi were identified. Cultures of the lung biopsy specimen for aerobic and anaerobic bacteria, mycobacteria, mycoplasma, chlamydia, *Legionella*, fungi, and viruses were negative. Groin abscess material contained numerous neutrophils and Gram-positive cocci and grew *S. aureus*.

Antibiotics were continued, and over the next week, the patient's respiratory status gradually improved as did the groin abscesses. An immunologic workup was done, and after 23 hospital days, patient was sent home on oral TMP/SMZ (5 mg/kg per day of TMP component) and dicloxacillin (12 mg/kg per day).

After discharge, the patient experienced monthly bouts of otitis media and frequent oral and diaper candidiasis. At 9 months of age, 3 days after discontinuing dicloxacillin, she was hospitalized with bilateral otitis media, high fever, and toxicity. Blood cultures were negative and the fever and toxicity disappeared promptly after institution of cefuroxime therapy. She was discharged and completed a 10-day course with cefaclor and then continued daily dicloxacillin along with TMP/SMZ. She has subsequently experienced no illness requiring hospitalization, nor has she had recurrence of pneumonia or cutaneous abscesses.

Although facies were thought initially to have been normal, the patient subsequently developed coarse facial features consistent with those reported previously in some HIE syndrome patients.⁽³⁾

Initial immune workup done during hospitalization at 4 months of age revealed elevated IgE for age (76 IU/+el) and poor neutrophil chemotaxis. Assays for lymphocyte markers and

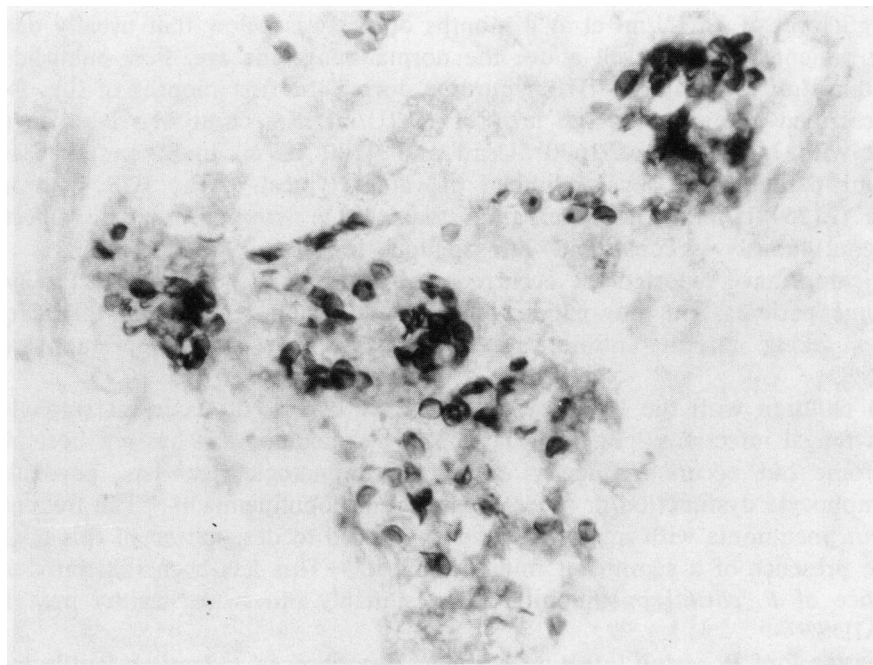


FIG. 1. Photomicrograph of methenamine silver-stained section of pulmonary tissue from an open lung biopsy done at 4 months of age. Numerous cysts and trophozoites of *Pneumocystis carinii* are evident. (Magnification, 500X).

proliferation were normal except for low lymphoproliferative responses to candida and PHA. Neutrophil chemotaxis analysis showed absence of chemotactic ability using zymosan-activated serum as chemoattractant, but random migration (chemokinesis) was normal.

Repeat neutrophil chemotaxis at 5 months of age remained abnormal but became normal at 10 months. No plasma inhibitors or serum chemotactic factor inactivators were present, and ability of the patient's serum to generate chemotactic activity was normal. Intracellular bactericidal assay at 10 months showed marginal to poor neutrophil killing of *S. aureus* 502A in the presence of either normal control or autologous sera. Intracellular killing at 17 months of age was normal.

Neutrophil chemiluminescence (phagocytosis associated and PMA stimulated) was low normal. Aggregation of neutrophils was normal in the presence of zymosan-activated serum or f-Met-Leu-Phe, and shape change of the patient's neutrophils in response to f-Met-Leu-Phe was normal.

Repeat lymphocyte analysis at 17 months of age was normal except for mildly depressed lymphocyte proliferation in response to candida and tetanus antigens. Also at 17 months of age, skin testing showed the presence of delayed-type hypersensitivity to candida antigen.

Serum levels of IgE were repeated at 9, 10, 17, and 20 months of age and were 590, 2125, 2200, and 7500 IU/ml, respectively. Antibody to human immunodeficiency virus was negative in an enzyme-linked immunosorbent assay.

DISCUSSION

Our patient represents the first reported case of *P. carinii* pneumonia associated with the HIE syndrome. Other than *P. carinii* pneumonia, the clinical and laboratory findings in our patient were consistent with published descriptions of the HIE syndrome, including multiple staphylococcal abscesses, staphylococcal otitis media, mucocutaneous candidiasis, eosinophilia, exaggerated IgE levels, depressed candida-induced blast transformation, and an intermittently demonstrable neutrophil chemotactic defect.

The initial IgE level of 76 IU/ml at 4 months of age was below that usually described for HIE syndrome patients but was well above the normal range for age. Few published data are available regarding IgE levels in the HIE syndrome during the first months of life. Donabedian and Gallin⁽³⁾ described a cord blood IgE level of 72 IU/ml in a child who later developed the HIE syndrome with IgE levels of 1600 IU/ml and 4100 IU/ml by 2 and 3 years of age, respectively. Our patient's IgE levels climbed to values typical of the HIE syndrome by 10 months of age (2125 IU/ml). The observation that the *in vitro* chemotactic defect was not demonstrable continuously is consistent with previous reports.^(3,13-15)

Other investigators have reported the occurrence of exaggerated IgE levels in family members of HIE syndrome patients, and our patient's father was found to have an IgE level of 6000 IU/ml and was taking chronic antibiotics because of previous recurrent staphylococcal abscesses.^(3,16-18)

Infections in children with the HIE syndrome usually consist of recurrent staphylococcal or mucocutaneous fungal infections.⁽⁴⁾ Pneumonia caused by pneumocystis has not been reported in the HIE syndrome but occurs frequently in other immunologic disorders, particularly those involving T-lymphocyte dysfunction or severe hypogammaglobulinemia.^(19,20) The frequent association of *P. carinii* pneumonia with immunodeficiency has led to designation of this organism as a sentinel for the presence of a significant immune defect.⁽²¹⁾ This has been illustrated recently in that the presence of *P. carinii* pneumonitis in presumably otherwise healthy men led to the discovery of AIDS.^(22,23)

One of the patterns of *P. carinii* infection has been described as endemic infantile pneumonitis and usually occurs in premature, debilitated, marasmic infants between 2 and 6 months of age.⁽²¹⁾ Our patient was neither premature nor did she have evidence of wasting, which often precedes the respiratory symptoms. The absence of the typical features of the endemic infantile

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pattern of pneumocystis in our patient prompted the investigation of her lymphocyte markers and function.

Previous investigations of T-lymphocyte subsets in HIE syndrome patients have produced varying and inconsistent results. Church⁽²⁾ reported a child with diminished numbers of circulating T lymphocytes. Two groups of investigators reported low numbers of circulating suppressor T cells,^(7,8) while others found no quantitative abnormality.⁽²⁰⁾

Abnormalities of lymphocyte function have been described, including altered lymphoproliferation in response to microbial antigens, poor anamnestic antibody responses to diphtheria and tetanus antigens, and variable results of delayed-type hypersensitivity skin testing.^(1-4,24) Mitogen-induced lymphoproliferative responses in HIE syndrome patients have usually been normal.⁽⁴⁾

Our patient's immunologic evaluation revealed no lymphocyte or antibody abnormalities that had not been recognized previously in HIE syndrome patients. The occurrence of *P. carinii* pneumonia in our patient underscores the potential additional significance of the lymphocyte abnormalities associated with the HIE syndrome. The contributing factors to the development of pneumocystis infection in our patient remain ill defined. Nonetheless, she has continued clinically well on dicloxacillin (12.5 mg/kg per day) and trimethoprim/sulfamethoxazole (5 mg/kg per day of the trimethoprim component) therapy.

Although our patient's cytomegalovirus infection appeared to be silent, it is conceivable that it contributed to her immune dysfunction. In the murine model of cytomegalovirus infection, defects in mouse neutrophil migratory and chemotactic activity were demonstrated.⁽²⁵⁾ However, human cytomegalovirus infection has not been associated unequivocally with neutrophil abnormalities.

Although our patient may remain unique, the occurrence of *P. carinii* pneumonia in our patient with the HIE syndrome should raise the index of suspicion for pneumocystis infection in other HIE syndrome patients with pneumonia, particularly infants. With a compatible clinical picture, consideration should be given for specific diagnosis by biopsy or bronchial lavage and early institution of appropriate anti-pneumocystis therapy. Further study will be required to define better the immunologic factors involved in the development of *P. carinii* pneumonia and to determine if other patients with the HIE syndrome are at increased risk of this infection.

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