

Case study

A 5-week-old HIV-1-exposed girl with failure to thrive and diffuse nodular pulmonary infiltrates

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A 5-week-old female infant with vertical HIV-1 exposure, progressive cough, and failure to thrive was given a diagnosis of bilateral diffuse nodular lung lesions. The child was without fever, leukocytosis, anemia, peripheral adenopathy, or hepatosplenomegaly, and the results of repeated blood tests for HIV-1 DNA were negative. A needle biopsy of the lungs revealed granulomatous inflammation and giant cells, with fungal organisms suggestive of *Aspergillus* species. A nitroblue tetrazolium dye test performed on the patient's blood specimen demonstrated absence of dye reduction, suggesting a diagnosis of chronic granulomatous disease. Further analysis revealed that the child had a deficiency of the p47^{phox} component of the nicotinamide adenine dinucleotide phosphate oxidase system. Thus this child with vertical HIV-1 exposure and diffuse pulmonary nodules actually had an autosomal recessive form of chronic granulomatous disease. This case study clearly demonstrates that children with suspected HIV-1 infection might also need evaluation for primary immunodeficiency and that the clinical immunology laboratory is a powerful adjunct in coming to a correct diagnosis. (*J Allergy Clin Immunol* 2004;113:627-34.)

Key words: Chronic granulomatous disease, HIV, pulmonary infiltrates, failure to thrive, infant

CASE PRESENTATION

An African American female infant who was perinatally exposed to HIV-1 was admitted to Texas Children's Hospital at 5 weeks of age for cough, poor weight gain, and vomiting.

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Abbreviations used

AR: Autosomal recessive
CGD: Chronic granulomatous disease
CRP: C-reactive protein
CT: Computed tomography
ESR: Erythrocyte sedimentation rate
LIP: Lymphocytic interstitial pneumonia
NADPH: Nicotinamide adenine dinucleotide phosphate
NBT: Nitroblue tetrazolium dye test
PLH: Pulmonary lymphoid hyperplasia
TMP-SMX: Trimethoprim-sulfamethoxazole

The patient had been well until 2 weeks of age, when she had a nonproductive cough that was worse at night and accompanied with post-tussive vomiting. Her appetite appeared good even after episodes of vomiting, but small, frequent feedings were better tolerated. She did not have fever, irritability, excessive sleeping, cyanosis, rash, jaundice, thrush, diarrhea, or history of travel out of the country. At 4 weeks of age, the patient was evaluated, and tests for HIV-1 infection were performed.

Her mother had been infected with HIV-1 for 6 years and had taken lopinavir-ritonavir, zidovudine, and lamivudine during pregnancy. She was clinically well, her viral load was undetectable, and her CD4 cell count was approximately 1000/mm³ at the time of delivery. She received intravenous zidovudine during the delivery. There was no history of immunodeficiency, tuberculosis, or severe recurrent infections in the family.

The infant was born at term through normal spontaneous vaginal delivery with a birth weight of 2997 g (10th-25th percentile) and began receiving zidovudine by mouth immediately after delivery. She was immunized with hepatitis B vaccine at birth. There was no history of exposure to tobacco smoke, pets, or farm animals.

The physical examination on admission to the hospital at 5 weeks of age demonstrated a well-appearing, alert infant with a weight of 3470 g (<5th percentile for age). The rectal temperature was 98.6°F, the pulse was 120 beats/min, and respiration was 40 breaths/min. The oxygen saturation was 98% to 100% on room air, and the patient was in no respiratory distress. Oropharyngeal

TABLE I. Results of hematologic and blood chemical tests in a female infant with HIV-1 exposure, failure to thrive, and modular pulmonary infiltrates: admission (5 weeks of age) and week 4 of antifungal treatment (11 weeks of age)

Variable	Age (wk)		Normal values*
	5	11	
Hemoglobin (g/dL)	11	11	9.5-13.5
Hematocrit (%)	33.4	32.4	29-41
White blood cells ($\times 10^3/\text{mm}^3$)	33.4	12.7	5-19.5
Differential cell count	B1 S33 L51 M11 E4	S31 L52 M10 E7*	S15-35 L40-72 M0-9 E0-7*
Platelet count ($\times 10^3/\text{mm}^3$)	543	436	150-450
CRP (mg/dL)	4.4	1.1	<1
ESR (mm/h)	61	18	0-20
Total protein (g/dL)	5	ND	5.6-7.2
Albumin (g/dL)	2.4	ND	3.9-5.1
Prealbumin (mg/dL)	4.7	8.8	18-44
Aspartate aminotransferase (U/L)	104	36	20-60
Alanine aminotransferase (U/L)	81	41	6-50
Gamma glutamyl transferase (U/L)	85	ND	11-82
Lactate dehydrogenase (U/L)	726	ND	500-920

B, Band neutrophil; S, segmented neutrophil; L, lymphocyte, M, monocyte, E, eosinophil; ND, not done.

*Normal values obtained from Texas Children's Hospital Department of Pathology Clinical Laboratory.

TABLE II. Virologic and immunologic test results

Variable	Patient age		Normal for age
	4 wk	6 wk	
HIV DNA PCR*	Negative	Negative	Negative
ALC (no./mm ³)	8428/49%	8190/45%	3400-7600/32%-72%†
CD3 (no./mm ³)	7248/86%	7207/88%	2500-5500/53%-84%†
CD4 (no./mm ³)	5647/67%	5405/66%	1600-4000/35%-64%†
CD8 (no./mm ³)	1686/20%	1638/20%	560-1700/12%-32%†
CD19 (no./mm ³)	506/6%	410/5%	300-2000/6%-32%†
IgG (mg/dL)	714	ND	251-906‡
IgA (mg/dL)	33.9	ND	1.3-53‡
IgM (mg/dL)	70.9	ND	20-87‡

ALC, Absolute lymphocyte count; ND, not done.

*Test result also negative at 4 months of age.

†Normal values taken from: Shearer WT, Rosenblatt HM, Gelman RS, Oyomopito R, Plaeger S, Stiehm ER, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the PACTG P1009 study. *J Allergy Clin Immunol* 2003;112:973-80.

‡Normal values obtained from Texas Children's Hospital Department of Pathology Clinical Laboratory.

examination revealed mild thrush, and the tympanic membranes were intact and without drainage. The lung and heart sounds were normal, and the abdomen was normal without organomegaly or masses. There were no palpable lymph nodes in the neck, axillae, groin, or other locations. Skin, musculoskeletal, and neurologic examinations were unremarkable.

Laboratory results showed an increased white blood cell count, increased eosinophils, mildly increased serum transaminases, and decreased prealbumin (Table I). Serum electrolytes, blood urea nitrogen, creatinine, and urine analyses were normal. Specimens from the nasopharynx were negative on the basis of rapid testing for respiratory syncytial virus and influenza, as well as on the basis of viral cultures.

A pyloric ultrasound examination that was performed on the day of admission was unremarkable. On the third day of admission, an upper gastrointestinal radiographic series revealed gastroesophageal reflux extending into the upper thoracic esophagus without visible aspiration or fistula. Multiple patchy opacities were seen in the lung bases, predominantly on the right, indicating the presence of multifocal nodular pneumonia. A radiographic swallowing function study was normal. A chest radiograph was obtained to review the lung infiltrates observed on the upper gastrointestinal series, which was again consistent with diffuse nodular infiltrates in both lungs. The size of the heart was normal. The thymus gland appeared normal.

Before hospitalization, because of the history of perinatal HIV-1 exposure, an HIV-1 DNA PCR test of the blood was performed at 4 weeks of age, and the result had been recorded as negative (Table II). At 6 weeks of age (within the first week of hospitalization), the results of a repeat HIV-1 DNA PCR test were again negative. Quantitative serum immunoglobulin levels (IgG, IgA, and IgM) and the numbers and percentages of CD4⁺ and CD8⁺ T-lymphocyte subpopulations were normal for age (Table II). Trimethoprim-sulfamethoxazole (TMP-SMX) was instituted for *Pneumocystis carinii* prophylaxis, and ranitidine was instituted for gastroesophageal reflux. Over the next few days, the cough and vomiting significantly improved. She remained afebrile and continued to tolerate oral formula feedings without respiratory difficulty.

Presuming that *Chlamydia* species-induced pneumonia might be the cause of the lung nodules on the chest roentgenogram, the patient was initially treated with erythromycin. However, she had bloody diarrhea without fever during the first week of erythromycin therapy, and stool cultures revealed *Clostridium difficile* toxin.

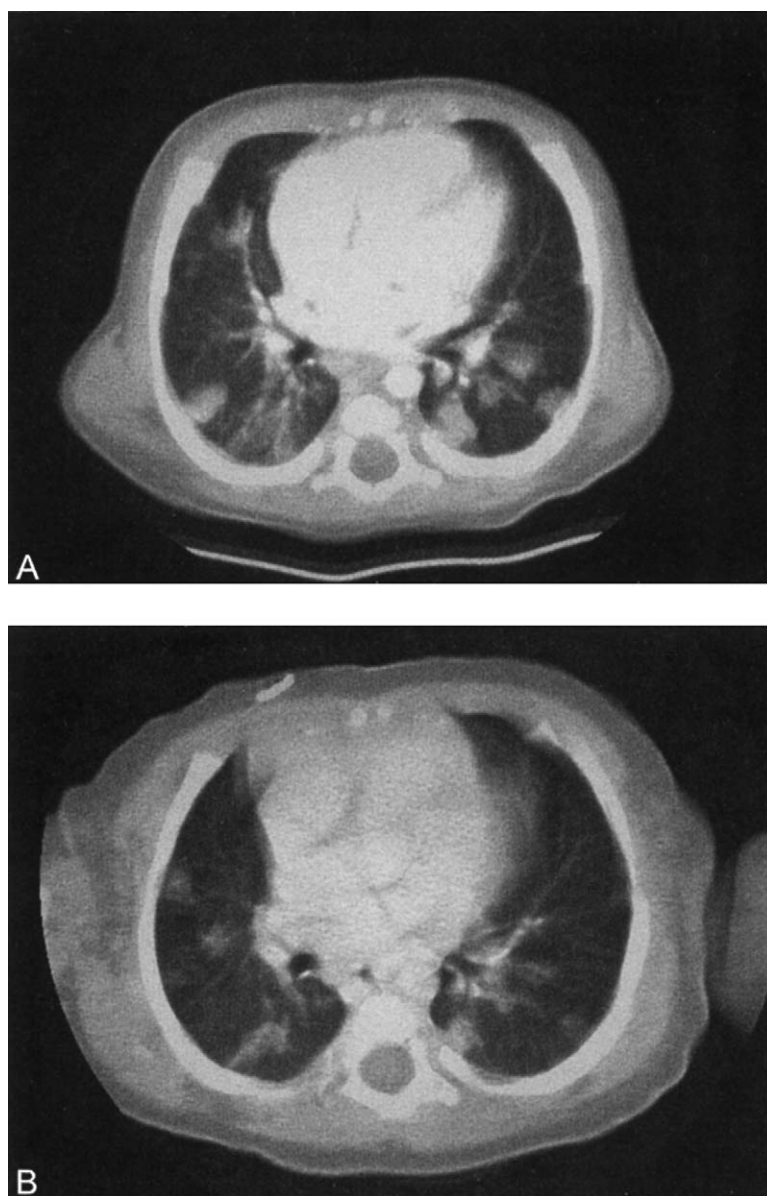


FIG 1. A, Pretreatment CT scan demonstrating multiple nodular opacities throughout both lung fields. **B,** CT scan showing improvement of nodular lung lesions 4 weeks after initiation of antifungal therapy.

Metronidazole was started, and the bloody diarrhea started resolving on the third day of the therapy. The serum *Chlamydia* IgM titer was less than 1:10, and erythromycin therapy was discontinued after 2 weeks. Repeat chest roentgenography at that time revealed no improvement in the diffuse nodular infiltrates. The serum C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) were increased at 4.4 mg/dL and 61 mm/h, respectively (Table I). Blood cultures were negative for legionella, mycobacteria, and bacterial, fungal, and viral pathogens. The serum EBV IgM titer and CMV antigen level were negative.

On the ninth day of hospitalization, a computed tomography (CT) scan of the chest, abdomen, and pelvis, obtained with administration of oral and intravenous

contrast material, revealed multiple nodular opacities throughout both lung fields. The largest of these was lying in the right costophrenic angle. Right pleural effusion and possible small left pleural effusion and subcarinal, axillary, and hilar lymphadenopathy were also noted (Fig 1, A).

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

This 5-week-old perinatally HIV-1–exposed infant girl was admitted with failure to thrive, vomiting, and a progressive cough that was not associated with respiratory distress or signs of hypoxemia. Her vomiting, as well as

her cough, responded well to antireflux medication. However, increased acute-phase reactants and the presence of bilateral diffuse nodular lung opacities on the chest roentgenogram primarily suggested an underlying infectious cause.

In considering the possible diagnoses in this infant, we first focused on those associated with HIV-1 and, subsequently, other possible pathogens. Interstitial pneumonitides, particularly lymphocytic interstitial pneumonia (LIP)/pulmonary lymphoid hyperplasia (PLH) complex, pulmonary alveolar proteinosis, and respiratory infections caused by *Pneumocystis carinii*, CMV, and tuberculosis, have been described in the first year of life in children born to HIV-1-infected women.¹⁻⁵

LIP is regarded as both a disease and a nonneoplastic inflammatory pulmonary reaction to various external stimuli or systemic disease. It is often seen with a variety of autoimmune syndromes and systemic immunodeficiency states, such as common variable immunodeficiency, agammaglobulinemia, and HIV-1/AIDS.⁶ A case of LIP has also been described in a 3-month-old infant who did not have HIV-1 infection.⁷ LIP/PLH complex is the most commonly reported chronic lung disease in HIV-1-infected children, and 16% to 50% of those with HIV-1 infection acquire it in the second or third year of life.⁸ In an original case series of the 28 HIV-1-infected children with chronic lung disease, 16 (57%) were found to have LIP.² In another study performed retrospectively on 66 children with HIV-1 infection, in 52% of all patients, a pulmonary problem was the first symptom of HIV-1 infection, and LIP/PLH occurred in 22% of these patients.⁹ LIP/PLH has been reclassified into category B from class C in the 1994 revised classification system for HIV-1 infection in children less than 13 years of age because it conveys a better prognosis.¹⁰ The distinction between LIP and PLH is made histologically. A characteristic histopathologic feature of LIP is a diffuse polyclonal infiltrate of small lymphocytes, plasma cells, and histiocytes surrounding airways and expanding the lung interstitium.^{6,11} In PLH the infiltration is primarily adjacent to the bronchial and bronchiolar walls and consists of bronchial-associated lymphoid tissue hyperplasia.¹² Association of LIP/PLH complex with EBV has also been reported.¹³ The onset is insidious, and the course is slowly progressive. Dry cough, tachypnea, dyspnea, and failure to thrive are common presenting symptoms.¹⁴ Generalized lymphadenopathy, hepatosplenomegaly, finger clubbing, and parotid gland enlargement are other physical findings associated with this disorder in its chronic state.¹² A retrospective case study performed on 95 vertically HIV-1-infected children revealed that admission to hospital rates caused by acute respiratory tract infection were significantly higher in children with LIP/PLH than in children without LIP/PLH.⁵ Increased serum immunoglobulin levels, especially those greater than 2500 mg/dL, are strongly associated with LIP/PLH.¹² The diagnosis is usually clinical, with supportive radiographic changes. Chest radiography and CT typically show bilateral diffuse reticulonodular infiltrates, with or

without areas of consolidation.^{15,16} In a prospective study it has been shown that reticulonodular changes on chest radiographs might be observed before 12 months of age.¹⁷ Despite the diffuse reticulonodular changes observed on the chest radiograph and CT scan, our patient did not present with any signs of respiratory distress together with her cough. She also did not have the organomegaly, finger clubbing, or parotid gland enlargement commonly associated with LIP/PLH complex, although she was only 5 weeks of age, and this condition might not have had sufficient time to develop.

Most pediatric cases of HIV-1 infection occur as the result of perinatal transmission. In the absence of maternal antiretroviral treatment and breast-feeding, the risk for HIV-1 infection among infants born to HIV-1-infected mothers is approximately 25%.¹⁸ The timing of transmission greatly affects the ability to accurately diagnose HIV-1 infection among infants during the first weeks or months of life.¹⁸ Perinatally acquired HIV-1 infection shows 2 distinct patterns: 10% to 15% of infected infants have a profound immune deficiency during the first few weeks of life and eventually have opportunistic infections and growth problems, sometimes along with encephalopathy. The remainder gradually have immune deficiency over a period of several years.^{19,20} Failure to thrive might be the first presenting symptom in children infected with HIV-1 in utero because of rapid progression to symptomatic disease.^{21,22}

Could our patient have been vertically infected with HIV-1? The mother had received prenatal care, and the mother's blood tests for HIV-1 viral load (undetectable) and CD4⁺ cell count (1000/mm³) suggested that she had taken her antiretroviral drugs. Most of the HIV-1-infected infants who have positive HIV-1 cultures or positive HIV-1 DNA PCR results at birth have different clinical characteristics from those who are not infected. They are 3 times more likely than average to have manifestations, such as hepatomegaly, adenopathy, splenomegaly, and smaller head circumference.²⁰ Our patient did not have hepatomegaly, splenomegaly, lymphadenopathy, or rash. She did have failure to thrive caused by recurrent coughing and vomiting episodes; however, these symptoms resolved gradually, and she started gaining weight after starting on ranitidine therapy and with frequent feedings and addition of protein powders into her milk formula. Infection with HIV-1 is characteristically associated with hypergammaglobulinemia in both pediatric and adult patients. In 2 different studies, most of the babies with HIV-1 infection showed an early abnormality in humoral immunity, consisting of hypergammaglobulinemia, and this abnormality was observed before clinical symptoms appeared.^{23,24} Our patient had age-appropriate serum immunoglobulin levels (Table II). Moreover, she had one negative HIV-1 DNA PCR blood test result obtained before this hospitalization when she was 4 weeks old. The second HIV-1 DNA PCR result was also negative at 6 weeks of life, with an above-normal CD4⁺ cell count for age caused by lymphocytosis (Table II). Infants are

considered to have in utero HIV-1 infection if the above-mentioned virologic test results are positive within 48 hours of birth and subsequent results are positive. If diagnostic test results for HIV-1 are negative within the first 48 hours of life and if subsequent test results are positive, then the non-breast-feeding infants are considered to have intrapartum HIV-1 infection. Recommended guidelines for the diagnosis of neonatal HIV-1 infection suggest that virologic assays be performed less than 48 hours after birth, between 1 and 2 months of age, and between 3 and 6 months of age. HIV-1 infection is confirmed if the infant has 2 consecutive virologic assay results that are positive.²⁵ Despite the initial suspicion that the patient might have been infected with HIV-1, the results of the virologic and immunologic assays, as well as her clinical status, were not consistent with pulmonary infection caused by HIV-1-induced immunodeficiency.

Three features of this case narrow the diagnostic possibilities: the gradual onset of respiratory symptoms and nonprogressive pattern of the disease; the absence of hypoxemia despite a radiographic pattern of marked, persistent, bilateral, diffuse nodular lung lesions; and the absence of fever, leukocytosis, anemia, peripheral adenopathy, and hepatosplenomegaly in the face of an increased ESR and CRP level.

The 2 most common causes of multiple nodules in the chest in infants are granulomas and pulmonary metastases. Granulomas are more common and include tuberculous and fungal infection.²⁶ A sample of lung tissue is needed to differentiate between these entities in this patient. On hospital day 14, a needle biopsy of the lungs was performed.

LABORATORY AND OTHER TESTS-PROCEDURES

On histopathologic examination, a section of the fine-needle biopsy of the right lower lobe of the lung showed myxoid fibroconnective tissue and a portion of granuloma (not shown). The granuloma was composed of epithelioid histiocytes, rare giant cells, lymphocytes, eosinophils, and macrophages without necrosis. No organisms were seen in this limited lung specimen. A CD1a stain was performed to determine whether any of the histiocytic cells could represent Langerhans cell histiocytes, and such cells were not identified.

Evidence of granulomatous inflammation and giant cells in the absence of organisms raised a suspicion of a neutrophil disorder. On hospital day 17, a nitroblue tetrazolium dye test (NBT) was performed from the infant's blood specimen that demonstrated absence of dye reduction in all neutrophils when compared with control cells, suggesting a diagnosis of chronic granulomatous disease (CGD). The glucose-6-phosphate dehydrogenase level was normal. A repeat NBT revealed only slight dye reduction (5%), which further confirmed the initial diagnosis. Screening of her parents with NBT revealed normal results. On hospital day 27, the patient underwent

a second fine-needle biopsy of the right lung because of negative cultures from the first biopsy, which demonstrated small portions of fibrous connective tissue and lung with a focally acute and diffusely chronic inflammatory infiltrate. On this second specimen, granulomas characterized by clustering of epithelioid histiocytes surrounding focal areas of necrosis and a few multinucleate giant cells were noted (Fig 2, A). Occasional eosinophils were also present within the inflammatory infiltrate. The methenamine silver stain showed rare and degenerating fungal organisms, with branching points suggestive of *Aspergillus* species (Fig 2, B). Acid-fast bacilli were absent. Cultures of both of the biopsy specimens have remained negative up to date for acid-fast bacilli, fungus, and yeast. Immunoblotting performed to define the molecular pathology in our patient revealed deficiency of the p47^{phox} component of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex (Fig 3).

TENTATIVE DIAGNOSIS WITH DISCUSSION OF PATHOGENESIS

CGD is characterized by a genetically heterogeneous defect of one of the subcomponents of the reduced NADPH oxidase system of phagocytes. The defect results in a reduced ability to produce antimicrobial reactive oxygen metabolites and is responsible for the impaired ability to kill intracellular microorganisms.^{27,28} In two thirds of patients, the inheritance is X-linked, caused by mutations affecting the membrane-bound gp91^{phox} (phox, phagocyte oxidase). In the remaining one third of the patients, the inheritance pattern is autosomal recessive (AR) caused by mutations in the genes encoding the phagocyte oxidase components p47^{phox}, p67^{phox}, and p22^{phox}.²⁹ Patients with CGD are susceptible to recurrent, severe, life-threatening infections with a subset of catalase-producing organisms, leading to abscesses or granulomas involving lymph nodes, bones, lungs, skin, the digestive tract, and the liver. The most common pathogens include the *Aspergillus* species (pneumonia), *Staphylococcus aureus* (suppurative adenitis, subcutaneous infections, and liver abscess), *Serratia* species (osteomyelitis and pneumonia), *Nocardia* species, and *Burkholderia cepacia* (pneumonia and sepsis).³⁰⁻³²

Aspergillus species are ubiquitous environmental molds that are a major cause of morbidity and mortality in patients with CGD.^{31,33,34} The lungs are the most common site of infection with *Aspergillus* species, and infected individuals commonly present with diffuse nodular pneumonia with peripheral alveolar opacities and localized pleural thickening.³⁵⁻³⁷ Although *Aspergillus* species are the most common fungal pathogen isolated, a significant minority of patients with CGD will have serious infections with unusual saprophytic fungi.³⁸⁻⁴⁰ The mean age at diagnosis of CGD is 3 years with the X-linked form and 7.8 years with the AR form. In that respect our patient was given a diagnosis of the AR form of CGD at a very early age.

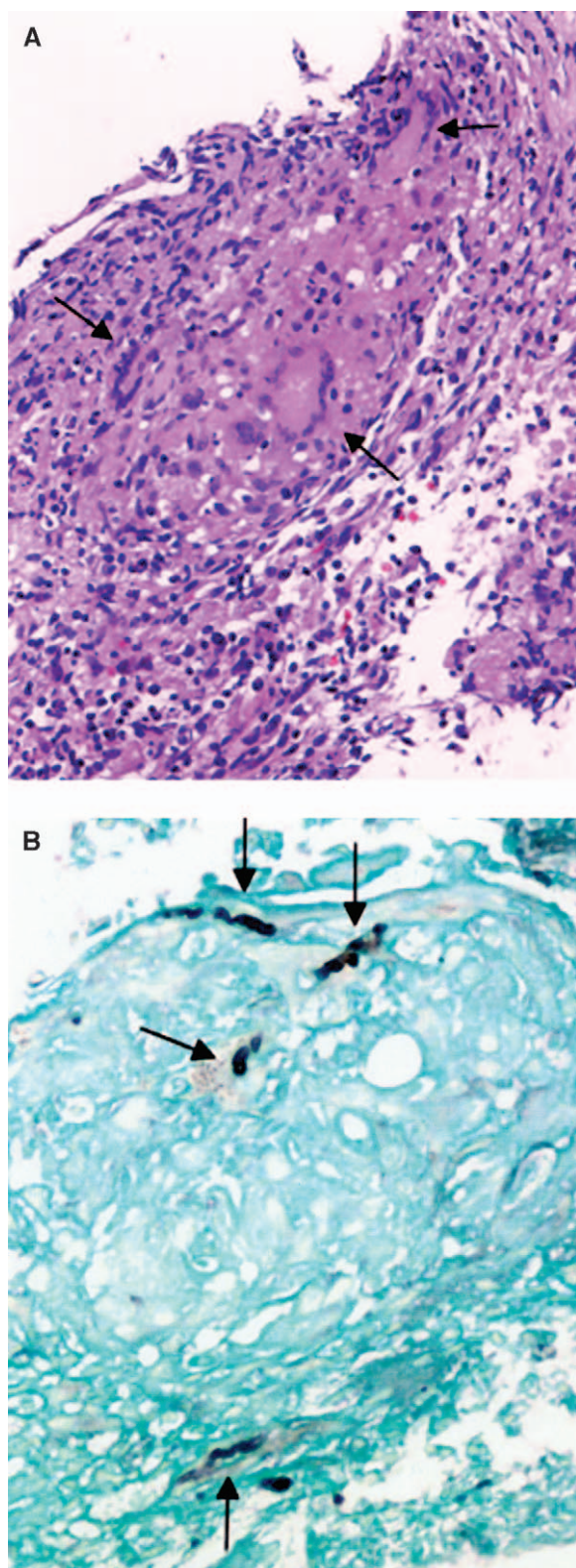


FIG 2. A, Lung specimen showing granulomatous inflammation consisting of epithelioid histiocytes and multinucleated giant cells (hematoxylin-eosin stain, arrows). B, Methenamine silver stain of the granuloma demonstrating rare and degenerating fungal hyphae (arrows).

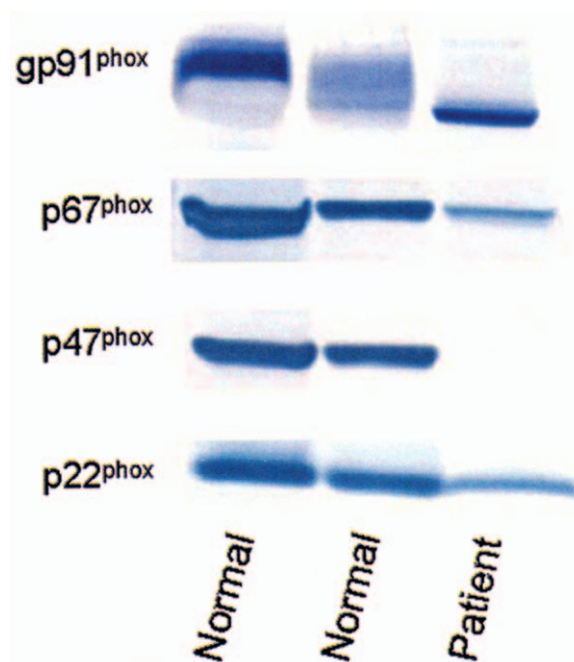


FIG 3. Immunoblot analysis of neutrophil lysates probed for each of the 4 structural components of the NADPH oxidase complex demonstrating deficiency of the p47^{phox} component, courtesy of Dr Douglas B. Kuhns, Science Applications International Corporation, Frederick, Md.

To our knowledge, this is the second reported case of CGD in an infant with vertical HIV-1 exposure. The first patient, a 2-year-old boy with a history of perinatal HIV-1 exposure, was initially diagnosed with Sweet syndrome (acute febrile neutropenic dermatosis) and later was found to have CGD.⁴¹ CGD has also presented in infancy in the form of multiple pulmonary nodules in the absence of HIV exposure⁴² as an early manifestation of granulomatous infiltration of tissues.⁴³

FINAL DIAGNOSIS AND TREATMENT-MANAGEMENT PLAN

The patient was given a final diagnosis of CGD because of a deficiency of the p47^{phox} component of NADPH. The patient received a 40 mg/kg cumulative dose of amphotericin B, after which the ESR, CRP level (Table I), and CT scan of the chest (Fig 2, B) were dramatically improved. She was started on itraconazole to receive a total of 6 months of antifungal therapy, after which she will receive lifelong prophylaxis. Although the needle biopsy of her lungs demonstrated septated hyphae consistent with *Aspergillus* species, the culture has been negative up to date. Radiographic improvement of lung nodules with amphotericin B further helped us to confirm our diagnosis.

Additional therapies that are routine in patients with CGD include the use of TMP-SMX once or twice daily to prevent bacterial infections and IFN- γ injections 3 times per week to decrease risk of infection. Our patient received

TMP-SMX prophylaxis and will receive IFN- γ injections when her weight has increased to more than 10 kg.

SUMMARY STATEMENT

This case study illustrates the complexity of making a diagnosis of primary immunodeficiency in the AIDS era. At present, there are approximately 6000 to 7000 babies being born to HIV-1–infected mothers each year in the United States, and the number of HIV-exposed babies is growing.⁴⁴ Although the percentage of HIV-1 infection in such infants is less than 1% because of the success of antiretroviral therapy of the mother and prophylactic treatment of the infant for 6 weeks, the index of suspicion must be extremely high for HIV-1 infection when babies, such as the one reported here, present with failure to thrive, weight loss, and lymphoid interstitial pneumonitis. By systematically using the power of the laboratory and diagnostic procedures, such as lung biopsy and pathologic examination, diagnostic imaging studies, and molecular examination for gene defects, a true diagnosis was attained. The clinical immunologist trained to diagnose primary immunodeficiency might indeed find children with these disorders in a growing cohort of children suspected of having the secondary immunodeficiency, HIV-1 infection. This case study has taught the attending physicians; residents in allergy and immunology, pediatrics, and medicine; and medical students a powerful lesson that time will never erase.

CLINICAL PEARLS FOR CASE STUDY

- Children with perinatal HIV-1 exposure might have primary immunodeficiencies.
- *Aspergillus* infection and CGD should be considered in the differential diagnosis in infants and children who present with diffuse nodular pulmonary infiltrates.
- Use of the clinical laboratories is essential for making the correct diagnosis.

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