We report the first case of HIV infection in a patient with underlying X-linked chronic granulomatous disease (CGD) who presented with hepatopulmonary nocardiosis. Despite the coexistence of CGD and HIV, the response to therapy was normal, and no unusual sequelae were noted. The patient’s high virus burden was successfully repressed with antiretroviral therapy, suggesting that the nicotinamide adenine dinucleotide phosphate oxidase system is not essential for active viral replication or response to antiretroviral agents.

Chronic granulomatous disease (CGD) results from genetic defects of the cellular nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system that lead to defective production of toxic oxygen metabolites by phagocytes. In two-thirds of patients, the inheritance is X-linked, caused by mutations affecting the membrane-bound gp91<sup>phox</sup> (phagocyte oxidase). In the remaining one-third of patients, the inheritance pattern is autosomal recessive secondary to mutations in the genes encoding the oxidase components p47<sup>phox</sup>, p67<sup>phox</sup>, and p22<sup>phox</sup> [1]. Patients with CGD are particularly susceptible to infections from the catalase-producing organisms <i>Staphylococcus</i>, <i>Burkholderia</i>, <i>Serratia</i>, <i>Nocardia</i>, and <i>Aspergillus</i> species [2].

Advanced HIV infection causes a progressive defect in cellular immunity with decreasing numbers of CD4<sup>+</sup> T lymphocytes, resulting in infections from opportunistic pathogens. Increased susceptibility to bacterial infections, attributed to complex T-cell, B-cell, and neutrophil dysfunction, has also been observed [3].

<i>Nocardia</i> infections are almost exclusively seen in immunocompromised patients. In reported series, 60%–90% of patients had some underlying immunosuppressive condition such as chronic steroid use, solid-organ transplantation, lymphoreticular malignancy, CGD, or HIV infection [4]. <i>Nocardia asteroides</i> is the predominant species and the one most commonly associated with disseminated disease. Typical sites of dissemination include the lungs, skin, brain, and musculoskeletal system. Less-common sites include the pericardium, kidney, adrenal glands, eye, spleen, and liver.

We report a case of simultaneous CGD and HIV infection with hepatopulmonary <i>Nocardia</i> infection. The patient had experienced a complete recovery from his <i>Nocardia</i> infection after treatment with trimethoprim-sulfamethoxazole (TMP-SMX) and ceftriaxone and to date has not had a recurrence while receiving continued TMP-SMX chemotherapy during the >4 years since his initial diagnosis. Despite the unique combination of the 2 immunodeficiencies, his clinical course has so far been conventional with respect to both the AIDS-related and CGD-related manifestations, although his estimated progression from seroconversion to AIDS was faster than average.
Figure 1. CT images of the chest and liver of a patient with HIV infection and X-linked chronic granulomatous disease who presented with nocardiosis. A, B, Images obtained at admission showing pulmonary (A) and hepatic (B) lesions. C, D, Corresponding images obtained 4 years after diagnosis with Nocardia infection.

CASE REPORT

The patient was a 28-year-old man with X-linked CGD. The diagnosis of CGD was established when the patient was 13 years old, when he was diagnosed with Burkholderia cepacia pneumonia on the basis of examination of open lung biopsy specimen. His past medical history included multifocal bilateral pulmonary nocardiosis at age 24 years. At that point, results of his HIV serological tests were negative. The species of the organism could not be further identified, and he was treated successfully with iv amikacin and minocycline, with complete resolution. He also had an episode of Paecilomyces lilacinus cellulitis of the left wrist at age 25 years, for which he had received amphotericin B followed by itraconazole. His medical follow-up as an adult had been infrequent because of alcohol and drug abuse interfering with adherence to medication regimens and regular clinic visits.

The patient presented to the Warren Grant Magnuson Clinical Center of the National Institutes of Health (NIH) with temperatures to 40.0–40.5°C, chills, fatigue, and cough with yellowish sputum for 2 weeks. He also had diarrhea and mild abdominal pain, predominantly in the right lower quadrant. At admission, he was febrile (39.7°C), with inspiratory crackles and egophony over the right lower lobe. A nontender erythematous nodule overlying the left wrist was also observed. The patient admitted to recent frequent use of iv administered cocaine. He used alcohol and tobacco regularly. Several of his family members also had CGD, and several female relatives were carriers.

Imaging studies and blood cultures were performed, and an HIV serologic test was ordered. Chest X-ray at admission confirmed a right lower lobe infiltrate. CT scan of the chest and abdomen showed consolidation of the right lower lobe with air bronchograms, central cavitation, and hilar and subcarinal lymphadenopathy (figure 1A). Several small hepatic abscesses were also detected (figure 1B).

CT-guided fine-needle aspirates of both the lung and liver lesions revealed gram-positive, modified acid-fast bacillus–positive filamentous organisms consistent with Nocardia species. Cultures of the sputum as well as of the lung and liver aspirates were positive for Nocardia species. Biochemical testing to identify the species was performed at the NIH and the Centers for Disease Control and Prevention (CDC) but was in-
The recent virus burden was currently elected not to receive antiretroviral agents. His most recent viral burden was 324,000 copies/mL (bDNA version 2, Chiron). He received zidovudine (300 mg b.i.d.) and lamivudine (150 mg b.i.d.) with indinavir (800 mg t.i.d.). Zidovudine was changed to stavudine (40 mg b.i.d.) because of neutropenia and nausea. Granulocyte transfusions were administered 5 days a week for 3 consecutive weeks while he was an inpatient. He became afebrile, and the pulmonary and hepatic lesions were improved at the time of follow-up imaging studies. His virus load fell to <10,000 copies/mL and his CD4+ count rose to 170 cells/mm³. He was discharged on subcutaneous IFN-α (7.5 mg/kg every 12 h) and ceftriaxone (2 g daily). Examination of a punch biopsy specimen of the lesion on his left hand showed fungal elements, and culture of the specimen grew Paecilomyces lilacinus. Amphotericin B therapy at a dose of 0.7 mg/kg per day was initiated. CT images of the brain appeared normal, and a bone scan did not show osteomyelitis.

The patient remained febrile. The dosage of iv TMP-SMX was decreased to 5 mg/kg every 12 h because of the patient’s decreasing neutrophil count. His serologic HIV test was positive, the CD4+ T lymphocyte count was 109 cells/mm³, and the virus burden was 324,000 copies/mL (bDNA version 2, Chiron). He received zidovudine (300 mg b.i.d.) and lamivudine (150 mg b.i.d.) with indinavir (800 mg t.i.d.). Zidovudine was changed to stavudine (40 mg b.i.d.) because of neutropenia and nausea. Granulocyte transfusions were administered 5 days a week for 3 consecutive weeks while he was an inpatient. He became afebrile, and the pulmonary and hepatic lesions were improved at the time of follow-up imaging studies. His virus load fell to <10,000 copies/mL and his CD4+ count rose to 170 cells/mm³. He left the hospital precipitously against medical advice after receiving a 5-week course of iv administered antibiotics (TMP-SMX and ceftriaxone).

Subsequent follow-up was erratic. He continued taking a double nucleoside regimen without a protease inhibitor because of his poor compliance, and orally administered TMP-SMX was taken twice daily. A regimen containing nevirapine was administered 5 days a week for 3 consecutive weeks while he was an inpatient. He became afebrile, and the pulmonary and hepatic lesions were improved at the time of follow-up imaging studies. His virus load fell to <10,000 copies/mL and his CD4+ count rose to 412 cells/mm³ (figure 2). When his virus burden rose, he was prescribed abacavir (300 mg b.i.d.), didanosine (200 mg b.i.d.), and ritonavir (100 mg b.i.d.) + indinavir (800 mg b.i.d.) combination therapy. Compliance with the new regimen was poor. At age 32 years, he developed severe thoracic spine pain after stopping all of his medications for several months. An Aspergillus fumigatus epidural abscess was diagnosed and debrided, and a prolonged course of amphotericin B followed by voriconazole was given. He was discharged on sc IFN-γ 3 times a week and orally administered TMP-SMX once daily. He has currently elected not to receive antiretroviral agents. His most recent virus burden was >500,000 copies/mL, and his CD4+ T cell count was 144 cells/mm³.

**DISCUSSION**

Systemic *Nocardia* infections occur more frequently in immunocompromised patients, including patients with CGD and AIDS. Injection drug use has also been suggested as an independent predisposing factor, probably because of direct inoculation of the organism into the bloodstream [5]. Prophylactic treatment with TMP-SMX does not seem to be fully protective in either CGD- or HIV-infected patients. In the series of 22 episodes of *Nocardia* infection in 19 patients with CGD reported by Dorman et al. [6], 45% of the patients were receiving TMP-SMX at the time of diagnosis and 30% were receiving IFN-γ. Uttamchandani et al. [7] reviewed 30 cases of *Nocardia* infection in HIV-infected patients in Miami, Florida, and reported an incidence of 1.8% (higher than previous reports), underscoring the significance of geographic variation. The same authors found a strong association of *Nocardia* infection with injection drug use [7]. All the cases were caused by *N. asteroides*, and the majority of the patients had pulmonary involvement. The mean CD4+ count in their cohort was 109 cells/mm³.

The English-language literature contains a description of only 1 case of *Nocardia brasiliensis* infection in the liver in a patient with HIV [8]. Two cases of *Nocardia* infection with liver involvement have been reported in patients with CGD. The first was in a 30-year-old man with X-linked CGD who had disseminated infection with *Nocardia transvalensis* that involved the lungs, liver, spleen, kidneys, and adrenal glands [9]. The second case was a 4-year-old girl with p47^phox^ deficiency who had osteomyelitis and a liver abscess [10]. Unfortunately, it was not possible to definitively identify the infecting species in the patient we studied, despite molecular and biochemical investigation at the NIH (Frank Witebsky, personal communication) and the CDC. There are scattered reports of liver involvement in cases of *Nocardia* infection in patients with [11–13] or without [14] immunosuppression. In a series of 63 isolates from...
France [15] and 29 isolates from Italy [16], liver involvement was reported in only 1 patient from each series.

The search for other concomitant infections in the immunocompromised host presenting with one infection was justified in this case, as has been suggested in the literature [17, 18]. Despite the initial suspicion that the patient’s wrist lesion represented a third focus of Nocardia infection, a fungal pathogen requiring different treatment was identified. More importantly, the search for a second acquired immune deficiency, such as HIV infection, should not be overlooked in patients with primary immunodeficiencies presenting with opportunistic infections. In the patient we studied, the presence of an HIV risk factor (injection drug use) suggested the diagnosis.

To our knowledge, this is the first reported case of HIV infection in a patient with CGD. Combined immunodeficiencies affecting different elements of the immune response may have additive or synergistic effects on overall rates of morbidity and mortality. Neutropenia and neutrophil dysfunction, including increased apoptosis, decreased chemotaxis, and decreased oxidative burst, have been described in patients with HIV infection [19–21], which contribute to the increased susceptibility to bacterial pathogens. The neutrophil impairment is more evident in patients with advanced disease (CD4+ count <200 cells/mm3) [22]. An association was reported recently between high HIV virus load (>10,000 copies/mL) and decreased neutrophil oxidative burst as measured by intracellular rhodamine 123 in a cross-sectional study of 160 HIV-infected patients [23]. This observation is further supported by studies showing improvement of neutrophil function after initiation of highly active antiretroviral therapy (HAART) [24, 25]. Klebanoff and Coombs [26] investigated the role of H2O2 produced by the respiratory burst of neutrophils in relation to HIV-1 in vitro. They found a neutrophil viridical effect mediated by the reaction of H2O2 with peroxidase and halide. When neutrophils from a patient with CGD were used in the same experimental conditions, the viridical effect was not seen. More recently, it was demonstrated that HIV-1 long-terminal repeat (LTR) introduced in Jurkat cell lines was activated by neutrophil respiratory burst–derived H2O2 [27]. Again, neutrophils from a patient with CGD did not have the same effect and did not lead to LTR activation.

In summary, this patient’s course has so far been uneventful with respect to AIDS-related opportunistic infections or malignancies, and his response to antiretroviral agents, when he complied with his drug regimen, was satisfactory. The additional burden of defective cellular immunity has not so far affected the manifestations of his underlying CGD. Further, the course of his virus burden and his response to antiretroviral therapy suggest that the NADPH oxidase system and the neutrophil oxidative burst are not essential components of efficient viral replication or successful suppression of HIV viremia by means of HAART.

References


