

Pneumococcal Vaccine Failure in an HIV-Infected Patient with Fatal Pneumococcal Sepsis and HCV-Related Cirrhosis

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Abstract

Pneumococcal vaccination of HIV-positive individuals is recommended to prevent pneumococcal infection. We present a case of a 44-year-old HIV-infected male who came to the emergency room with bacterial pneumonia and sepsis. The patient also had a history of HBV and HCV infection. He expired in the emergency room and blood cultures were positive for *Streptococcus pneumoniae*. The autopsy confirmed the clinical diagnosis and, in addition, hepatitis C-related cirrhosis and splenic abnormalities. The patient had no history of opportunistic infections. His CD4 count 3 months prior to coming to the emergency room was 216 cells/ μ L with a viral load of 1,270 copies/mL. The patient had received Pneumovax™ two years before his death. The organism isolated from blood cultures was *Streptococcus pneumoniae* isotype 3, a strain included in Pneumovax. This is a case of pneumococcal vaccine failure with a fatal outcome in a person with an HIV infection and hepatitis C-related liver cirrhosis.

Key Words: *S. pneumoniae*, isotype 3, vaccine, Pneumovax, HIV, pneumonia, sepsis, HCV, cirrhosis.

Introduction

BACTERIAL PNEUMONIA, particularly secondary to *Streptococcus pneumoniae*, is a common and life-threatening manifestation of AIDS (1–3). A commonly used polysaccharide vaccine, Pneumovax™, represents antigens of 23 different strains of *S. pneumoniae* and covers about 82–85% of all pathogenic strains (1, 3). Vaccination against *S. pneumoniae* is recommended for patients with HIV infection (4), but it has been shown that such patients have a variable response to pneumococcal vaccine (5). In fact, at least 6 cases of vaccine failure have been reported in people with HIV infection and in patients with AIDS (6–11). This is a report of a case of Pneumovax failure in a previously asymptomatic HIV-positive person with concurrent hepatitis C-related cirrhosis, who expired secondary to pneumococcal sepsis and pneumonia.

Case

A 44-year-old Caucasian male presented in April 1997 to the emergency room (ER) with a

6-day history of violent shaking chills, night sweat and malaise; he reported shortness of breath, occasional blood-tinged sputum and pleuritic chest pain for three days. The patient was known to have been HIV-positive for 8 years, with risk factors including intravenous drug abuse. He had received medical care at the infectious disease clinic in this hospital. At his last appointment, 3 months prior to his presentation to the ER, he had a CD4 cell count of 216 cells/ μ L (17%) and a CD4/8 ratio of 0.27; 6 months prior to presenting to the ER, his CD4 count was 235 cells/ μ L (16%) and his viral load was 1270 copies/mL. He had a history of chronic sinusitis and hepatitis C and a complete recovery from hepatitis B infection; he had never suffered from the opportunistic infections common in AIDS. For two years prior to his ER presentation, he had been taking zidovudine, lamivudine and trimethoprim-sulfamethoxazole.

In the ER the patient was poorly cooperative, appeared pale and coughed occasionally. His respiratory rate was 40/min. The patient was hypotensive (BP 91/60 mm Hg) and his heart rate was 114/min. He was afebrile, hypoxemic and oliguric. The breath sounds over the right lung field were decreased, and the chest X-ray showed an infiltrate of the entire right lung. Septic shock with severe bacterial pneumonia was diagnosed. Ceftazidime, erythromycin, trimethoprim-sulfamethoxazole and intravenous hydration were administered. Lab-

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oratory studies showed thrombocytopenia, toxic granulation of leukocytes, slight target cells and crenated cells on the blood smear, and acute renal failure. The prothrombin time was prolonged (14.5 seconds) and the patient had increases in AST (234 U/L) and ALT (94 U/L). The serum total protein and albumin were 5.3 and 2.1 gm/dL respectively. Subsequent studies showed worsening of hypoxemia, metabolic acidosis and an elevated lactate level. The patient required orotracheal intubation and mechanical ventilation. About 11 hours after presenting to the ER, the patient developed recurrent ventricular tachycardia and expired.

An autopsy showed lobar pneumonia, pleural effusion, ascites, cardiomegaly with unremarkable valves, esophageal varices, splenomegaly and hepatomegaly with liver cirrhosis. Histopathology of the lungs revealed sheets of acute and chronic inflammatory cells diffusely filling the alveolar spaces, intra-alveolar edema and capillary congestion. Histopathology of the liver revealed cirrhotic micronodules surrounded by bridging bands of fibrosis with portal ductular proliferation and moderately periductal lymphocytic infiltrate. Histopathology of the spleen showed marked sinusoidal congestion with mild depletion of the white pulp. Lymph nodes showed mild follicular depletion. With the exception of minimal aseptic leptomeningitis, the neuropathological findings were unremarkable.

Streptococcus pneumoniae was cultured from various blood samples. The organism was sensitive to penicillin, chloramphenicol, vancomycin and erythromycin. Isotyping confirmed *S. pneumoniae*, strain type 3.

Subsequent review of the infectious disease clinic chart revealed that the patient had received Pneumovax™ (Merck, Sharp and Dhome) and vaccination for influenza virus two years before his death. The polyvalent pneumococcal vaccine also includes isotype 3. At the time of vaccination his CD4 count was 250 cells/ μ L (19%); he was prescribed zidovudine, lamivudine and trimethoprim-sulfamethoxazole. Over the subsequent 2 years there was a transient increase of his CD4-count to a maximum of 370 cells/ μ L (22%) and then a slow decline.

Discussion

We present a case of an HIV-infected host who quickly succumbed after the onset of pneumococcal pneumonia despite having received Pneumovax some two years earlier. Six cases have been previously reported with pneumococ-

cal vaccine failures in people with HIV or patients with AIDS (6–11). Previous cases included one patient with a CD4 count of 500 cells/ μ L, who expired with pneumococcal meningitis about 18 months after vaccination. The isolate identified was *S. pneumoniae* isotype 9, which is included in the vaccine (6). Another case involved a patient with a CD4 count of 141 cells/ μ L at the time of vaccination; this patient succumbed to pneumococcal meningitis with isotype 3 approximately 13 months after vaccination (7). A further case concerns a patient with a helper T-cell count of 13% and a helper/suppressor ratio of 0.22; the patient succumbed to pneumonia, with isolation of *S. pneumoniae* type 4, *Pneumocystis carinii* and *Legionella pneumophila*. Evaluation of stored serum specimen from all three patients showed poor antibody response to vaccination (6–8). Unfortunately, sera needed to examine the post-vaccination antibody response were not available in our patient. The other reports (9–11) of pneumococcal vaccine failure in HIV-infected persons do not give details about serotype of the organism and immune status of the host.

Several lines of evidence suggest a humoral defect in HIV-infected people; they have been reported to generate poor antibody response to pneumococcal vaccines (5,12–15). Sera obtained from HIV-negative adults vaccinated with a 23-valent vaccine showed increased *in vitro* killing activity against certain *S. pneumoniae* isotypes, when compared with the sera of HIV-positive patients with actual pneumococcal infections (9). Furthermore, only 67% of the HIV-infected patients to whom Pneumovax had been administered showed a significant increase of specific IgG and IgG2 one month after vaccination. In these patients, specific antibodies returned to prevaccination levels 12 months after vaccination (15). This indicates that prophylaxis Pneumovax in HIV-infected patients is transitory, with a significant number of such patients being non-responders (15). The anti-pneumococcal antibody response seems to be regulated by T-cell derived cytokines (16). Similarly, measles vaccination yields lower antibody response in vaccinated HIV-positive children than in vaccinated healthy children (17). Finally, patients with AIDS have been reported to generate a poor B-cell response to pneumococcal polysaccharide (tetradecavalent) and protein (keyhole-limpet hemocyanin) (14). The post-Pneumovax antibody response to isotype 3 is particularly impaired in HIV-positive patients (12). This is especially serious, since

isotype 3 has a high case fatality rate even with antimicrobial therapy (18). Identification of the isotype in reports of pneumococcal vaccine failure in HIV infections or AIDS include *S. pneumoniae* isotype 3 (this report and ref. 7), 4 (ref. 8), 6 (ref. 11) and 9 (refs. 6 and 11).

Our case demonstrates the potential seriousness of pneumococcal infection in patients with HIV infection. Pneumococcal bacteremia has a particularly high mortality in AIDS patients (2). A previous report indicated a good outcome of pneumococcal bacteremia in HIV-infected individuals without AIDS compared to those with AIDS (19). While we believe that our patient did not fit the exact criteria for AIDS some 3 months earlier, we cannot exclude the possibility that, at the time of his admission, the CD4 count had dropped below 200 cells/ μ L. Thus, he might have fulfilled the diagnostic criteria for AIDS. In addition, he had hepatitis C liver cirrhosis with depletion of the lymphocyte population in the spleen and lymph nodes, and thus might have been additionally immunocompromised. Prior studies have showed the essential role of the spleen in the clearance of pneumococci from the bloodstream (20, 21). In the previously described case, even though the CD4 count was reported as 500 cells/ μ L, information on the CD4 percentage was missing (6). It has been shown that CD4 percentage shows less variability and has greater prognostic significance than the absolute CD4 count (22, 23), particularly in the setting of splenectomy in HIV-infected patients (24). Comorbidities placing the patient at risk for pneumococcal infections cannot be ruled out in the absence of an autopsy. Our patient had chronic sinusitis and may have been colonized with *S. pneumoniae*, with an increase in risk for recurrent infections.

The patient presented here had, in addition, autopsy-proven hepatic cirrhosis, most likely due to hepatitis C virus infection. Hepatitis C virus infection is a common infection in HIV-positive patients (25–27). Resistance to *S. pneumoniae* and specific antibody response has been studied in animal models (28, 29). Cirrhotic rats are able to generate a specific type 3 pneumococcal capsular polysaccharide antibody response (29) which is even higher than in non-cirrhotic control animals. However, challenge with type 3 pneumococci was associated with a higher mortality in vaccinated cirrhotic rats than in control animals, and elicited a greater post-challenge response in control animals than in cirrhotic animals. Thus “the increased serum concentrations of functional,

type-specific anticapsular antibody in vaccinated cirrhotic rats does not reverse their impaired resistance to type 3 pneumococcal pneumonia” (29). Moreover, compared to control animals, cirrhotic rats display decreased phagocytosis of *S. pneumoniae* by polymorphonuclear leukocytes in the lung and increased phagocytosis by alveolar macrophages (30). Cytokines and serum complement levels are altered in cirrhotic animals and patients (28, 31). These mechanisms might play a role in patients with HCV-related liver cirrhosis and might be complicated with concurrent HIV-infection as in our patient. However, very little is known about pathogenesis of bacterial infections in concurrent HIV/HCV infection.

Recent reports show that influenza virus impairs immune function and that influenza infection may precede severe pneumococcal pneumonia in previously healthy children (32). There is no evidence that our patient had a concurrent influenza infection. He received his last influenza vaccination 2 years prior to the presentation.

Furthermore, zidovudine has been reported to improve the response to pneumococcal vaccine in persons with AIDS (33, 34). At the time of vaccination, our patient was prescribed zidovudine and lamivudine. A previously reported case of pneumococcal vaccine failure received zidovudine 10 months after Pneumovax (7); antiretroviral therapy was not mentioned in other reports of pneumococcal vaccine failure (6, 8). The temporal relation of anti-retroviral therapy and vaccination may influence the degree of antibody response to the vaccine. Our patient had not received protease inhibitors or non-nucleoside reverse transcriptase inhibitors. These medications, used in various combinations, have been shown to restore general immune competence (23) and to decrease morbidity and mortality in patients with AIDS (35). It is worthwhile exploring whether Pneumovax response increases with the use of these potent antiretroviral combinations. One might consider the optimal timing of Pneumovax administration in relation to the initiation of antiretroviral therapy.

Pneumococcal vaccine failure is particularly serious, since drug-resistant pneumococci have become more prevalent in recent years (36).

In the future, monitoring of the antibody response before and after vaccination might help to identify a subpopulation of HIV-infected people who show a low antibody response. Improved vaccines and vaccine schedules, restoring immune function with advanced anti-retroviral therapies, and revaccination should all be

considered, to prevent and/or reduce the morbidity and mortality of HIV-infected individuals with pneumococcal infections.

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