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Case report

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Recurrent pneumococcal meningitis in a splenectomised HIV-infected patient

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Abstract

Background: *Streptococcus pneumoniae* is a major cause of human disease, especially in pre-school children and elderly people, as well as in special risk groups such as asplenic, antibody deficient patients, or presenting disruption of natural barriers. The occurrence of pneumococcal disease has increased with the onset of the HIV epidemic and the emergence of drug-resistance.

Case presentation: We report the case of an HIV-1-infected patient who experienced three episodes of recurrent pneumococcal meningitis over a 4-year period, despite chemoprophylaxis and capsular vaccination.

Conclusions: Efficacy of anti-pneumococcal chemoprophylaxis and vaccination in HIV-infected patients are discussed in the light of this particular case.

Background

Streptococcus pneumoniae is a Gram-positive, encapsulated bacterium that is a major human pathogen, predominantly in young children and elderly people, as well as in patients presenting with asplenia, sickle cell disease, and inherited or acquired immunodeficiencies [1]. In industrialized countries, where vaccination against *Haemophilus influenzae* type b is widespread, *S. pneumoniae* has become a major cause of bacterial meningitis, together with *Neisseria meningitidis*, and bacterial meningitis is now a disease predominantly of adults rather than of infants and children [2,3]. In the developing world, bacterial meningitis remains a major problem, with increased incidence and mortality compared to more developed countries [4,5]. With the onset of the HIV pandemic and the worldwide emergence of drug-resistant pneumococci, the incidence of invasive pneumococcal infection has increased in adults as well as children [6–9], and pneumococcal vaccine was recommended in the USPHS/IDSA guidelines for the management of HIV-infected patients. We report the case of an HIV-infected patient who experienced three episodes of recurrent pneumococcal meningitis over a 4-year period, despite anti-pneumococcal vaccination and chemoprophylaxis.

Case presentation

A 29 year-old patient was found to be HIV-1-infected through investigations for an idiopathic thrombocytopenic purpura in 1989. After unsuccessful medical treatments, splenectomy was performed and anti-pneumococcal chemoprophylaxis (phenoxymethylpenicillin, 2 MU/day) was carried out until 1996. Meanwhile, a series of HIV-related infections occurred: *Pneumocystis carinii* pneumonia in 1993, herpetic esophagitis, herpetic anorectal lesions and cutaneous Kaposi's sarcoma in 1995, CMV retinitis, *Mycobacterium avium* complex infection, facial *molluscum contagiosum* and catheter-borne septicaemias due to *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*. Since the rifabutin anti-*M. avium* treatment would also be efficient against pneumococcal infections, the specific anti-pneumococcal prophylaxis was stopped in 1996. After several lines of mononucleoside therapy, a combination of stavudine, lamivudine and nelfinavir was started in 1997, the biological efficacy of which allowed the interruption of the prophylactic ganciclovir treatment in December 1998, and that of cotrimoxazole in March 1999.

The first episode of pneumococcal meningitis (Table 1) occurred in 1998, and was successfully treated with the association of cefotaxime (12 g/day, 17 days) and vancomycin (3 g/day, 12 days). The pneumococcal strain isolated from the CSF belonged to serotype 23F and exhibited a decreased susceptibility to penicillin (Minimal Inhibitory Concentration (MIC) = 1.0 μg/ml), and was resistant to erythromycin and clindamycin. A bilateral maxillary sinusitis diagnosed a few weeks before was considered as the likely portal of entry. No specific anti-pneumococcal prophylaxis, which had been stopped two years earlier, was prescribed at that time.

Two and a half years later, in 2000, a second meningitic episode occurred. Blood and CSF cultures yielded the presence of a serotype 23F pneumococcal strain, with identical antibiotic susceptibility to that of the first episode (Table 1). The patient was successfully treated using ceftriaxone (2 g/day) and vancomycin (2 g/day). Although no pneumococcal carriage or distant focal infection could be detected, chemoprophylaxis was reintroduced (phenoxymethylpenicillin, 3 MU/day). Furthermore, the patient received the 23-valent capsular pneumococcal vaccine (Pasteur Vaccins, Lyon, France).

Six months later, the patient was admitted in intensive care unit for meningitis. Culture of the CSF showed the presence of a serotype 23F *S. pneumoniae* that was resistant to penicillin (MIC = 2 μg/ml), but susceptible to ceftriaxone (MIC 0,75 μg/l). Successful treatment was obtained using ceftriaxone (6 g/day) and vancomycin (2 g/day) for 15 days. Radiology imaging of the mastoids and of the skull did not show any abnormal sign, and neither pneumococcal carriage nor concomitant infection could be detected. Radio-isotopic imaging disclosed no breach of the meninges. After antibiotic treatment was successfully completed, an anti-pneumococcal chemoprophylaxy was decided (amoxicillin 2 g/day), as well as conjugate anti-pneumococcal vaccination (Wyeth-Ayerst Laboratories, Philadelphia, PA, USA). The patient was monitored and has done well more than two years after this third episode.

Analysis by pulsed-field gel electrophoresis (PFGE) of *Sma*I-restricted genomic DNA of the first and the third isolates revealed that the restriction profiles were not distinguishable from each other, and were different from those obtained with unrelated pneumococcal strains from our collection (data not shown). Unfortunately, it was not possible to include the isolate responsible for the second episode in the PFGE study.

Together with the fact that the three pneumococcal isolates were of serotype 23F, PFGE analysis strongly suggests that both isolates belong to the same clone. Moreover, the three strains exhibited the same antibiotic resistance patterns, apart from an increased MIC to penicillin in the third isolate (Table 1). Therefore, it is very likely that the

Table 1: Biological characteristics of the three meningitic episodes

	Episode 1 (March 1998)	Episode 2 (May 2000)	Episode 3 (January 2001)
CSF characteristics	Glucose: not detectable Proteins: 3.2 g/l Leucocytes: 670/mm3 (96%PMN) Positive culture with *S. pneumoniae* 23F	Glucose: 1 mM Proteins: 2.9 g/l Leucocytes: 2100/mm3 (51%PMN) Positive culture with *S. pneumoniae* 23F	Glucose: 0.4 mM Proteins: 2.2 g/l Leucocytes: 8100/mm3 (85%PMN) Positive culture with *S. pneumoniae* 23F
Beta-lactam susceptibility MICs (μg/ml)	penicillin G: 1.0 amoxicillin: 0.75 ceftriaxone: 0.75	penicillin G: 1.0 amoxicillin: 0.75 ceftriaxone: 0.75	penicillin G: 2.0 amoxicillin: 0.75 ceftriaxone: 0.75
CD4 (10^6 cells/l – %)	325 – 13	1103 – 21	1185 – 20
Viral load (copies/ml – Log_{10})	280 – 2.5	1300 – 3.1	2000 – 3.3

three meningitic episodes were caused by the same pneumococcal strain, and that successive curative and prophylactic antibiotic treatments led to the selection of derivatives with decreased susceptibility to penicillin G.

Conclusions

In this case, the occurrence of three episodes of pneumococcal meningitis over a 4-year period highlights the controversial efficacy of vaccination and antibiotic prophylaxis in HIV-1-infected patients. Recurrent meningitis is a rare disease that is often associated with cranial injuries, and *S. pneumoniae* is responsible for more than half of the recurrent purulent bacterial meningoencephalitis [10]. The first episode was probably due to the bilateral maxillary sinusitis, as was already reported [11]. Furthermore, the infection with HIV-1 and the splenectomy were also shown to be additional risk factors [12–14,7]. However, at the time of anti-pneumococcal vaccination and before the third episode occurred, the patient had CD4+ cell count greater than 500 cells/μl, which was reported to decrease the risk of pneumococcal disease [7].

The patient was not receiving anti-pneumococcal chemoprophylaxis when the first and second episodes occurred. However, when the third episode occurred, the patient had been subjected to 23-valent capsular vaccination and was receiving chemoprophylaxis, as well as a biologically efficient antiretroviral treatment. Although the patient's compliance to the treatment could not be thoroughly assessed, this case highlights the uncertain efficacy of chemoprophylaxis [15], and differs from other previously reported cases in immunocompetent patients, where capsular vaccination and ampicillin prophylaxis were shown to reduce the recurrence rate of pneumococcal meningitis [16].

This observation also highlights the controversial effect of pneumococcal vaccination in HIV-infected patients. Some authors consider that potential benefit of capsular vaccination is greater than risk [17,18,7], and anti-pneumococcal capsular vaccination figures among the USPHS/IDSA recommended guidelines for the management of HIV-infected patients. However, other works have shown that 23-valent pneumococcal polysaccharide vaccination may be poorly effective in HIV-1-infected adults, especially among African-American persons and people in Uganda [18–22], and other reports suggested that it might be more cost-effective to concentrate efforts on anti-retroviral therapy [23]. Efficacy of vaccination in HIV-1-infected patients receiving HAART (Highly Active Anti-Retroviral Therapy) is poorly documented, but recent reports showed that pneumococcal capsular polysaccharide vaccination in such patients induces a qualitative change in antibody response compared with non-HAART-treated patients [24]. This involves an increased VH3-positive antibody response, which had been shown to be present in vaccine response of HIV-uninfected patients. Taken together, recommendations for use of non-conjugated pneumococcal polysaccharide vaccines in HIV-infected people should be re-assessed, particularly in the identification of sub-groups most likely to benefit from the vaccine [25].

The patient experienced no other recurrence of pneumococcal infection more than two years after vaccination with the conjugated heptavalent capsular vaccine. As well as the non-conjugated 23-valent capsular vaccine, this new generation of vaccine also covers serotype 23F, and was described to possibly interrupt the transmission of antibiotic-resistant *S. pneumoniae* among children [26]. Administration of conjugated vaccines in HIV-infected patients was reported to be safe, and to have no peculiar effect on viral load [27,28]. Furthermore, vaccination regimens that include pneumococcal conjugate vaccines lead to higher antibody concentration and greater functional antibody activity [27]. A trial of a 9-valent pneumococcal conjugate vaccine recently showed a potential efficacy in HIV-infected children, and suggest that such an approach should be investigated in HIV-infected adults [29]. However, further studies are needed to evaluate if conjugated capsular vaccines should be introduced in the systematic care of HIV-1-infected patients.

Authors' contributions

PCM, CP and PB supervised microbiological and molecular characterisation of patient samples, and participated in patient management. VV, BD, and JPV were in charge of patient management. EA and GQ carried out molecular biology experiments. PCM and VV drafted the manuscript.

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