Polyarticular Pneumococcal Infection in an Immunosuppressed Adult: A Case Report and Review of Literature

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Abstract
We report a 46-year-old immunosuppressed man who developed cervical spondylodiscitis, right coxofemoral septic arthritis and osteomyelitis of the right acetabulum secondary to a *Streptococcus pneumoniae* bacteremia in spite of being properly immunized according to the standard vaccination schedule. Recent studies have found no evidence of protection for high-risk patients immunized with the polysaccharide vaccine. Thus, the role of the vaccination schedule is also discussed.

ABBREVIATIONS

IPD: Invasive Pneumococcal Disease; BEACOPP: Bleomycin, Etoposide, Doxorubicine, Cyclophosphomide, Vincristine, Procarbazine, Prednisone; MRI: Magnetic Resonance Imaging; ESR: Erythrocyte Sedimentation Rate; CRP: Chain Reaction Polymerase; HIV: Human Immunodeficiency Virus; ANA: Antinuclear Antibodies; ANCA: Anticytoplasm of The Neutrophil Antibodies; RF: Rheumatoid Factor; APCC: Anti-Cyclic Citrullinated Peptide Antibodies

INTRODUCTION

Osteoarticular involvement caused by *Streptococcus pneumoniae*, an infrequent complication included in the spectrum of invasive pneumococcal disease (IPD), is uncommon among healthy adults [1, 2], whilst bacteremia by this microorganism is frequent in immunosuppressed patients or those with chronic diseases. There are several factors, such as ageing, chronic diseases, HIV infection, neoplasms, solid organ or hematopoietic cell transplantation and some treatments (i.e. chemotherapy or biologic agents) that impair the host immunological response and predispose to IPD development [3]. Vaccination is the main strategy to prevent its appearance. A correct vaccination schedule, including 13V vaccine, should be performed in order to prevent IPD in high-risk patients.

We describe a splenectomized patient due to Hodgkin’s lymphoma (nodular sclerosis variant, stage IV-B), diagnosed after splenectomy in 2008. He was treated with a BEACOPP protocol (bleomycin, etoposide, doxorubicine, cyclophosphomide, vincristine, procarbazine, prednisone), and remained in complete remission since 2010. After surgery the patient received the standard vaccination schedule (anti-Haemophylus influenzae serotype b, anti-Neisseria meningitidis serogroup C, anti-pneumococcal polysaccharide 23V). A second dose of anti-pneumococcal polysaccharide 23V vaccine was given in 2011. In June 2012, he was diagnosed with bilateral avascular necrosis of the femoral head, and surgery had been planned three months earlier, because of severe pain. At this time, an exodontia had been performed because of caries lesions and no prophylactic antibiotic was indicated. His current medications included tramadol and paracetamol.

At admission, his temperature was 39ºC, his blood pressure was 120/70 mmHg, and his heart rate was 70 b.p.m. He had gum disease and dental caries with several teeth affected. The patient complained about pain to palpation from C4 to C6 spinous processes, with polyarticular infection secondary to *S. pneumoniae*. Bacteremia.

CASE PRESENTATION

A 46-year-old male was admitted to our Internal Medicine Department in December 2013, because of neck and right hip pain lasting for two weeks, along with high-grade fever (39ºC) in the last four days.

He denied any tobacco, alcohol, or illicit drug use. His past medical history included a Hodgkin’s lymphoma (nodular sclerosis variant, stage IV-B), diagnosed after splenectomy in 2008. He was treated with a BEACOPP protocol (bleomycin, etoposide, doxorubicine, cyclophosphomide, vincristine, procarbazine, prednisone), and remained in complete remission since 2010. After surgery the patient received the standard vaccination schedule (anti-Haemophylus influenzae serotype b, anti-Neisseria meningitidis serogroup C, anti-pneumococcal polysaccharide 23V). A second dose of anti-pneumococcal polysaccharide 23V vaccine was given in 2011. In June 2012, he was diagnosed with bilateral avascular necrosis of the femoral head, and surgery had been planned three months earlier, because of severe pain. At this time, an exodontia had been performed because of caries lesions and no prophylactic antibiotic was indicated. His current medications included tramadol and paracetamol.

At admission, his temperature was 39ºC, his blood pressure was 120/70 mmHg, and his heart rate was 70 b.p.m. He had gum disease and dental caries with several teeth affected. The patient complained about pain to palpation from C4 to C6 spinous processes, and he had a significant functional limitation on the right lower extremity. The remainder of the physical examination was unremarkable.
Table 1 showed the main laboratory parameters at admission. Blood cultures were initially obtained and the patient was then started on intravenous cloxacillin (2g/6h) and gentamicin (240 mg/d), and oral naproxen (500 mg/12 h). A magnetic resonance imaging (MRI) of the cervical region showed a C6-C7 spondylodiscitis with an epidural abscess extending from C4 to T1. No myelopathy was observed (Figure 1).

Twenty-four hours after admission, Streptococcus pneumoniae grew in the blood cultures, and antibiotics were shifted to intravenous cefotaxime (2g/6h). A transthoracic echocardiogram showed no evidence of infective endocarditis. An orthopantomography showed that teeth 35 and 36 were affected by caries lesions, and exodontia was performed.

Nasopharyngeal carriage of S. pneumoniae was ruled out through a negative nose and throat swab. Noteworthy, serum anti-pneumococcal antibodies level was 215 µg/ml (normal value: >2000 µg/ml), and lower serum IgM levels were found (Table 1). Other causes of secondary immunodeficiency were ruled out, and laboratory markers of autoimmunity were negative (Table 1).

The clinical outcome was favourable, fever disappeared and neck pain improved, although the patient still reported pain at the right hip, initially thought to be related to his avascular necrosis. A plain radiograph did not show bone involvement. Nevertheless, a gallium-67 scintigraphy scan showed an intense uptake at the right coxofemoral joint consistent with septic arthritis and synovitis. MRI showed signs of avascular necrosis in both femoral heads and, on the right side, signs of arthritis, joint effusion, swelling of the bursa of the iliopsoas muscle and a loss of signal on T1, with enhancement after administration of contrast, at the level of the hip-socket medial subcondral bone, a typical feature of osteomyelitis (Figure 2). An ultrasonography-guided biopsy was performed, and a serofibrinous exudate was obtained. Microbiological studies of the synovial fluid were negative.

The isolate of S. pneumoniae was identified as serotype 6C. Cefotaxime was administered over 8 weeks, without any complication, and with complete clinical recover. A MRI performed at the end of treatment did not show any sign of infection. A dose of 13V anti-pneumococcal vaccine was then administered.

**DISCUSSION**

Streptococcus pneumoniae is an extra-cellular pathogen that usually colonizes the human nose and throat [4, 5]. IPD is defined by the isolation of Streptococcus pneumoniae in a sterile environment (blood, or cerebrospinal, pleural, peritoneal and synovial fluid) [6].

Due to the advances in antibiotic therapy and in the pattern of immunization over the last few decades, osteoarticular infection (arthritis, spondylodiscitis or osteomyelitis) caused by this bacteria has become a rare entity among healthy adults [1, 4]. Thus, septic arthritis is an infrequent complication of pneumococcal bacteremia (0.6-10% across series) [1, 4, 7, 8]. Despite what is usually thought, S. pneumoniae is a prevalent cause of bacterial arthritis [7]. On the other hand, pneumococcal vertebral osteomyelitis is a very rare condition, with an

### Table 1: Main laboratory results in the reported patient.

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count (x 10³)</td>
<td>17.8</td>
<td>4.8 - 10.8</td>
</tr>
<tr>
<td>Platelets (x 10⁹)</td>
<td>402</td>
<td>150 - 450</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>73.0</td>
<td>42.0 - 75.0</td>
</tr>
<tr>
<td>ESR (mm/1¹h)</td>
<td>80</td>
<td>1.0 - 15.0</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>31</td>
<td>0.1 - 0.5</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>0.6</td>
<td>&lt; 0.5 ng/mL</td>
</tr>
<tr>
<td>HIV 1/2</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

#### ADAPTIVE IMMUNITY

<table>
<thead>
<tr>
<th>Lymphocyte subsets (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3⁺</td>
</tr>
<tr>
<td>CD4⁺</td>
</tr>
<tr>
<td>CD8⁺</td>
</tr>
</tbody>
</table>

| Anti-pneumococcal antibodies (µg/ml) | 215 | >2000 µg/ml |

<table>
<thead>
<tr>
<th>Serum immunoglobulin (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
</tr>
<tr>
<td>IgA</td>
</tr>
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<td>IgG</td>
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<td>IgG1</td>
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<tr>
<td>IgG2</td>
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<tr>
<td>IgG3</td>
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<tr>
<td>IgG4</td>
</tr>
</tbody>
</table>

#### INNATE IMMUNITY (mg/dl)

| C3 | 226.0 | 77.0 - 203.0 |
| C4 | 33.1 | 7.7 - 50.5 |

#### IMMUNOLOGY

| ANA | Negative |
| ANCA | Negative |
| RF | Negative |
| APCC | Negative |

**Abbreviations:** ESR: Erythrocyte sedimentation rate; CRP: Chain reaction polymerase; HIV: human immunodeficiency virus; ANA: antinuclear antibodies; ANCA: anticytoplasm of the neutrophil antibodies; RF: rheumatoid factor; APCC: anti-cyclic citrullinated peptide antibodies.
incidence of 0.2-1.3% from series to series [17-20]. Regarding pneumococcal spondylodiscitis, the cases reported are scarce [9-13, 21]. Moreover, polyarticular involvement is present in up to 30-35% of cases of pneumococcal bacteremia [4, 16].

The primary source of pneumococcal arthritis is respiratory tract infection (usually pneumonia), following by middle ear involvement [14, 15]. Blood cultures are positive in more than 70% of the cases and synovial fluid cultures in 40-90% [2, 4, 16]. Nevertheless, Bullsey [22] found that 16% of the cases of pneumococcal septic arthritis were not associated with a clinically identified primary source of infection. In these cases, a transitory bacteremia secondary to the involvement of a mucous membrane should be the origin of the articular infection.

Our patient did not have any previous respiratory tract infection nor was a nasopharyngeal *S. pneumoniae* carrier. However, some serotypes causing IPD are either not detected or only identified prior to onset of the disease. Another issue is that nose and throat swabs were obtained after antibiotic treatment was started. Several studies [23-27] point to a lack of sensitivity of a single nasopharyngeal (NP) swab. Thus, Satzke et al. [28] recommendation is to collect a single NP swab in order to detect pneumococcal carriage, so taking a higher number of specimens at the same time does not significantly increase the sensitivity [28]. Considering these arguments, we cannot totally rule out the possibility of a false negative carriage in the case here reported.

Our patient had had an exodontia (without any prophylactic antibiotic treatment) 3 months before he becomes febrile. Therefore, the most probable source of the pneumococcal bacteremia in our patient, was the gingiva, a structure which is commonly colonized by this pathogen [9, 22].

Chronic diseases and immunosuppression are strong predisposing factors for the development of IPD. Our patient was diagnosed with Hodgkin’s lymphoma, his spleen was surgically removed and he had a bilateral avascular necrosis of femoral heads, conditions which increase the risk of developing IPD, in this case, in the form of osteoarticular disease.

Besides, we found a selective IgM deficiency, an uncommon disorder, defined by the absence of or an isolated serum IgM deficiency (<0.3 g/L) associated with normal levels of the rest immunoglobulins and a normal cellular immunity [29]. Patients with this disorder may remain asymptomatic, suffer repeated infections or develop autoimmune and/or neoplastic diseases. However, in our case, the lower IgM levels could be related to the absence of spleen, although we cannot rule out a primary origin since at the time of Hodgkin’s disease diagnosis, serum IgM levels were low (31 µg/mL).

Finally, another interesting issue in the case here reported is related to the anti-pneumococcal vaccine. In fact, vaccination is the main strategy to prevent IPD. Our patient had received two doses of 23V pneumococcal polysaccharide vaccine according to the standard schedule. Anti-pneumococcal antibodies were determined by using a WHO-recommended ELISA protocol for type-specific IgG antibodies to the pneumococcal polysaccharide vaccine (VaccZyme™ PCP IgG, Binding Site). Micro wells were coated with Pneumovax vaccine, containing 23 Streptococcus pneumoniae serotypes 1-5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F. The antibody response was lower than expected and not explained by a selective antibody deficiency. Serum total IgG and IgA levels were within the normal limits. Besides, impaired response to pneumococcal vaccine has been associated with lower serum IgG2 and IgA levels, the main IgG subclasses responsible for the development of antibodies against polysaccharide antigens. However, these serum IgG subclasses were normal in our patient. Therefore, the lower response to anti-pneumococcal vaccination in this case was probably related to splenectomy, and to the profile of activity of the 23V vaccine due to that two sequential 23V doses of pneumococcal polysaccharide vaccine are associated with an effect of immunological tolerance traduced in a hip responsiveness phenomenon.

In this sense, in Spain, there are currently two types of anti-pneumococcal vaccines available in adults. The polysaccharide vaccine (23V), used for people aged more than 2 years, includes the greatest number of serotypes (1, 2, 3, 4, 5, 6B, 7F, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F), but it does not generate immune memory, the levels of antibodies decrease with time, induces immune tolerance and does not act against nasopharyngeal colonization. A recent meta-analysis [30] showed that the effectiveness in IPD prevention of the 23V vaccine in healthy adults was 74% (IC95% 56-85%), and did not find evidence of protection for high-risk patients. This fact can be added to the previously mentioned causes explaining the lower levels of anti-pneumococcal antibodies found in our patient.

On the contrary, the conjugate vaccine (13V), approved in July 2013 by the European Medicines Agency for people over 18 years, does generate immune memory and a more powerful response than the polysaccharide vaccine in terms of the majority of the 13 serotypes included (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F), which accounted for 50-76% of cases of IPD in adults over 50 years [31]. Several clinical trials comparing the polysaccharide and conjugate pneumococcal vaccines in high-risk immunosuppressed individuals had found that conjugates vaccines induce a superior immune response than 23V vaccine [32-35].
In our case, the isolated S. pneumoniae serotype was 6C, which is not included in either of the two vaccines above mentioned. In fact, our patient was not immunized against this serotype. There are numerous studies that point to an increase in the incidence of IPD due to this serotype [36, 37]. Although none of the vaccines approved contains the serotype 6C, opsonophagocytic studies based on the serum of individuals receiving the 13V vaccine (the only vaccine that contains the serotype 6A, with a similar immunological structure to 6C serotype), have an in-vitro reaction to serotype 6C [38]. These studies also showed the in-vitro inefficiency of the serum of individuals receiving 23V vaccine in terms of eliminating serotype 6C. Therefore we can expect that 13V vaccine provide cross-protection against this serotype, although this may be speculative since none of the two vaccines provide coverage against serotype 6C.

In conclusion, we should bear in mind the particular clinical findings of pneumococcal osteoarticular infection. Its optimal prevention in high-risk patients should include the 13V conjugate vaccines providing coverage against serotype 6C. Although this may be speculative since none of the two vaccines provide coverage against serotype 6C.

REFERENCES


