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Meningitis, spondylodiscitis, pneumonia and septic shock with \textit{Streptococcus pneumoniae} in a previously healthy woman with isolated IgG2-, IgG3-, IgA-deficiency and monoclonal gammopathy of undetermined significance

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Abstract
A 66 years old Caucasian woman with pneumococcal meningitis was treated and discharged after an uncomplicated course. Five months later she was readmitted with fever and right side abdominal pain and diagnosed with pneumococcal spondylodiscitis. One year later she was treated for a severe chest X-ray confirmed left lobar pneumonia. Two years later she was diagnosed with a pneumococcal pneumonia in her left lung with septic shock. An immune deficiency screen revealed slightly reduced IgA levels, low IgG2 levels, low IgG3 levels and high IgG1 levels. No other immune defects were identified. She did not respond serologically on vaccination with 13-valent conjugate and 23-valent polysaccharide pneumococcal vaccines. Further evaluations revealed a positive M-component in her blood and a bone marrow biopsy diagnosed her to have monoclonal gammopathy of undetermined significance. To protect her against future life threatening pneumococcal infections she was started on treatment with intravenous immunoglobulin. The case report illustrates the importance of thorough evaluation of patients with unusual infectious disease entities or unusual frequency of infections in individual patients. To optimize prophylactic measures and active treatment options in the individual patient, it is important to identify underlying causes of diseases and immune deficiencies that potentially can lead to life threatening infections. This is illustrated in our case by an undiagnosed monoclonal gammopathy of undetermined significance in an apparently healthy woman with at least three life threatening documented pneumococcal infections in a two-year period and poor pneumococcal vaccine response.

Introduction
\textit{Streptococcus pneumoniae} is a common invasive pathogen with pneumonia, sinusitis, otitis and meningitis as common foci of infection. It is a rare etiology of spondylodiscitis and endocarditis. Underlying diseases and immune deficiencies can increase the risk of developing invasive pneumococcal infections.

Case Report
Pneumococcal infectious episode 1
A previously healthy 66 years old Caucasian woman was admitted acutely with reported fever at home, but afebrile (36.3 degrees Celcius) at arrival to hospital and with progressive confusion. Objective findings showed photophobia, confusion and terminal neck stiffness. She was circulatory stable. Her blood chemistry showed elevated infection parameters (CRP 197 mg/L and leucocytes 17.2×10^9/L). A spinal tap showed turbid cerebrospinal fluid (CSF) with pleocytosis (348×10^6/L) and 85% polynucleated leucocytes in the CSF. Levels of CSF protein was 3.9 g/L and of CSF glucose 0.8 mmol/L. The Gram stain of the CSF was negative. The patient was started in standard treatment for bacterial meningitis with intravenous Dexamethasone (10 mg × 4), intravenous Benzylpenicillin (1.8 g × 6) and intravenous Ceftriaxone (4 g × 1) according to Danish guidelines. The patient had received oral Phenoxyethylpenicillin from her General Practitioner before admission, and there was no bacterial growth in the CSF. However \textit{Streptococcus pneumoniae} (Serotype 15C) grew in one of four blood culture bottles sampled at the time of hospital admission. The isolate was fully susceptible to Penicillin. A Chest X-ray (CXR) at the time of admission revealed a small basal pulmonary infiltration on the left side. The patient responded very well to 10 days of high dose intravenous Benzylpenicillin (1.8 g × 6) treatment and was discharged after 10 days. She was discharged in the outpatient clinic for a further two months. After two months she was in her normal health status with normal blood chemistry and normal levels of infection markers. She returned to her normal work as a nurse.

Pneumococcal infectious episode 2
Five months later she was admitted again acutely with reported fever at home but afebrile (36.9 degrees Celcius) at arrival to hospital. She now had pain in her right side of the abdomen stretching to the lumbar back. In the emergency room her vital parameters were stable, the abdomen was soft with no abdominal guarding and she had normal bowel sounds. CRP (133 mg/L) and leukocytes (13.3 × 10^9/L) were elevated with neutrocytosis. Liver enzymes and alkaline phosphatases were normal. She did not appear septic and was not acutely ill. The clinical picture was quite uncharacteristic and this initiated several diagnostic procedures including CXR, CT-thorax and CT-abdomen with no positive findings. Her blood cultures were negative and she did
Case Report

using an in-house Luminex bead-based
Clinical Microbiology (Statens Serum
vaccination status was performed at the
against the pneumococcal serotypes includ-
indicating that they did not protect her
response to the pneumococcal vaccines
response showed inadequate vaccine
coccal spondylodiscitis she was again working full time as a nurse. After her
treatment for pneumo-
coccal spondylodiscitis was not kept after diagno-
sis. She was still without antibiotic treatment. A CT guided biopsy of the
involved spinal segment was performed and the
bone biopsy showed growth of Streptococcus pneumoniae. The isolate was
fully susceptible to Penicillin. The patient
was now started in treatment with intravenous Benzylpenicillin (1.2 g x 4). After
four weeks of intravenous treatment she
was switched over to oral Amoxicillin/Clavulanic Acid (500/125 mg x 3) for further 6 weeks, reaching a total
duration of antibiotic treatment of 10
weeks. The Streptococcus pneumoniae iso-
late identified in the bone biopsy from the
spondylodiscitis was not kept after diagno-
sis, so it has not been possible to serotype this isolate and verify if the two isolates from the meningitis and the spondylodisci-
tasis were of the same pneumococcal
serotype. A transthoracic echocardiography revealed normal heart valves without signs of endocarditis. No transesophageal
echocardiography was performed. The
treatment was successful and her inflamma-
tory biomarkers returned to normal levels after finishing her treatment for pneumo-
coccal spondylodiscitis.

Eight months after the last episode with pneumococcal spondylodiscitis, the patient
had no symptoms, no back pain and was again working full time as a nurse. After her
pneumococcal spondylodiscitis she was vaccinated with two pneumococcal vac-
cines within a period of 11 months (first 13-
valent conjugate pneumococcal vaccine Prevenar® and then 23-valent polysaccha-
ride pneumococcal vaccine Pneumovax®
). Blood testing for serological vaccine
response showed inadequate vaccine
response to the pneumococcal vaccines
indicating that they did not protect her
against the pneumococcal serotypes includ-
ed in both vaccines (Table 1). Control of
vaccination status was performed at the
Danish National Reference Laboratory for
Clinical Microbiology (Statens Serum
Institute, SSI, Copenhagen, Denmark)
using an in-house Luminex bead-based
assay. Antibody measurement of specific
anti-pneumococcal IgG antibodies to
serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C,
19A, 19F and 23F was performed. From the
geometric mean of the 12 serotype specific antibodies, the vaccination status of the
patient could be determined. After the sec-
ond episode of invasive pneumococcal
infection, the patient was evaluated for pos-
sible immune defects with measurements of
immunoglobulins, IgG subclasses and flow-
cytometric analyses of her leukocyte sub-
types. Low levels of IgG2, of IgG3 and of
IgA levels were observed (Table 2). Very
high levels of IgG1 was observed (Table 2).
CT-abdomen showed a normal spleen
and no signs of lymphoma. CT-thorax showed
no thymoma and no signs of lymphoma. No
immunological action was taken on these
observed low levels of IgG2, of IgG3 and of
IgA at this time.

Infectious episode 3

One year after her pneumococcal
meningitis she was treated by her General
Practitioner with oral antibiotics for a CXR
verified large pneumonia involving the left
down lobe. CRP was measured to 125 mg/L
by her General Practitioner. She was treated
with Penoxymethylpenicillin 1600 mg x 2
for 7 days with good clinical response. No
bacterial etiology was identified, but the
CXR was compatible with a classic lobar
pneumonia that could have been caused by
Streptococcus pneumonia.

Pneumococcal infectious episode 4

Two and a half years after her pneumo-
coccal meningitis she was admitted febrile
(39.2 degrees Celcius) with septic shock
and a CXR verified pneumonia. The CRP
was only 18 mg/L at arrival rising to 147
mg/L on the second day of admission. Her
leukocytes at arrival were 12.4 x 10^9/L with
neutrocytosis. Streptococcus pneumoniae
Serotype 21 was cultured from the sputum.
The isolate was fully susceptible to
Penicillin. Blood cultures were negative.
She was treated with Benzylpenicillin 1.2 g

<table>
<thead>
<tr>
<th>Pneumococcal serotype</th>
<th>September 2015</th>
<th>November 2015</th>
<th>May 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotype 1</td>
<td>0.18</td>
<td>0.05</td>
<td>0.61</td>
</tr>
<tr>
<td>Serotype 3</td>
<td>0.10</td>
<td>0.04</td>
<td>0.22</td>
</tr>
<tr>
<td>Serotype 4</td>
<td>0.06</td>
<td>0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>Serotype 5</td>
<td>0.08</td>
<td>0.04</td>
<td>0.14</td>
</tr>
<tr>
<td>Serotype 6B</td>
<td>0.12</td>
<td>0.04</td>
<td>0.28</td>
</tr>
<tr>
<td>Serotype 7F</td>
<td>0.33</td>
<td>0.12</td>
<td>0.59</td>
</tr>
<tr>
<td>Serotype 9V</td>
<td>0.43</td>
<td>0.13</td>
<td>0.28</td>
</tr>
<tr>
<td>Serotype 14</td>
<td>1.02</td>
<td>0.45</td>
<td>0.84</td>
</tr>
<tr>
<td>Serotype 18C</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>Serotype 19A</td>
<td>1.00</td>
<td>0.11</td>
<td>1.71</td>
</tr>
<tr>
<td>Serotype 19F</td>
<td>0.60</td>
<td>0.07</td>
<td>2.21</td>
</tr>
<tr>
<td>Serotype 23F</td>
<td>1.50</td>
<td>0.09</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Figure 1. T1 weighted magnetic resonance imaging of the spine without (A) and with (B) intravenous contrast, shows contrast enhancement in Th8, Th9 and in the discus between (with permission from the Department of Radiology, National Hospital Faroe Islands)
× 4 for 5 days and after that for ten days more with Phenoxymethylpenicillin 800 mg × 4. After the last episode with life threatening septic shock with a pneumococcal pneumonia as primary focus, immune deficiency screening (immunoglobulins, IgG subclasses and flowcytometric analyses of leucocyte subtypes) was repeated (Table 2) and based on observed persistent low levels of IgA, of IgG2 and of IgG 3, intravenous immunoglobulin substitution (IVIG) therapy was started (Privigen®). She still had very high IgG1 levels (Table 2). She had a negative HIV test and normal CD4 counts. She has not had any serious bacterial invasive infections since starting IVIG.

In October 2016, three and a half years after her pneumococcal meningitis, a blood test showed a positive M-component. The identified M-component was an IgG-kappa chain. The identified M-component in the blood led to a bone marrow biopsy performed in December 2016. The bone marrow biopsy gave the diagnosis of monoclonal gammopathy of undetermined significance (MGUS) with 5-10% plasma cells in the bone marrow biopsy. The patient is now followed in the hematological out-patient clinic for her MGUS and treated with IVIG to protect her against invasive infections.

Discussion and Conclusions

Streptococcus pneumoniae is a common pathogen, but pneumococcal meningitis followed by pneumococcal spondylodiscitis has been described rarely. In cases of bacteremia with Streptococcus pneumoniae, involvement of multiple organs should always be considered, especially in high risk patients (alcohol overconsumption, diabetes mellitus, immunosuppression and after splenectomy).4

Spondylodiscitis will typically have a subacute debut. Early symptoms can be unspecific and initially be back pain and fever like in our case report.5 Conventional X-ray examinations of the spine are often normal in the early phases of spondylodiscitis. Bone scintigraphy and MRI are sensitive early in the disease process and will typically give positive findings already after few days. MRI is still considered as the golden standard with a high sensitivity and specificity in diagnosing spondylodiscitis.6 PET-CT is getting an increasing role in the diagnosis of spondylodiscitis and well suited for patients with contraindications for MRI. It is important to make efforts in identifying the microbiological etiology in the cases of spondylodiscitis. Positive blood cultures with a pathogen known to be associated to spondylodiscitis, combined with imaging suggesting spondylodiscitis, is usually considered as enough to have proven the etiology of the spondylodiscitis, and start a relevant antibiotic treatment strategy based on the bacterial finding. With negative blood cultures, it is important to try to perform a diagnostic bone biopsy to identify the pathogen to plan the correct antibiotic treatment. Another important reason for the bone biopsy is excluding differential diagnoses as malignant disease in the spine or tuberculosis as the cause of the spondylodiscitis (Pott’s disease).5

The patient described in this case report suffered from two more severe pneumonias over the next two years after the episode of pneumococcal spondylodiscitis. This indicated that an underlying cause for infection including the possibility of immune deficiencies should be considered. An immune deficiency screening including measurements of immunoglobulins, IgG subclasses and flowcytometric analyses of the leucocyte subsets was performed. No leucocyte anomalies were observed and the CD4 count was normal, negative HIV test, negative SLE autoantibodies and no signs of lymphoma. Low IgG2 levels and low IgG3 levels were observed on several occasions, and slightly decreased IgA levels was also observed. The most common IgG subclass deficiency is low levels of IgG2 combined with low levels of IgA.6 The clinical significance of low IgG subclass deficiencies is still questionable. It is well known that levels of immunoglobulin and IgG subclasses can fluctuate significantly during infection. To make a definitive conclusion immunoglobulin levels should be measured repeatedly including in periods where the patient has no infection. It has been reported that patients with myelomatosis and MGUS have lower antibody levels against several bacteria including Streptococcus pneumoniae.7 Because of the combination of several severe life threatening pneumococcal infections, in this previously healthy nurse combined with the observation of low levels of IgG2, of IgG3 and of IgA over several years, a decision was made to treat her with IVIG therapy. The combination of low levels of IgG2, of IgG3 and of IgA, and at the same time very high IgG1 levels led us to think about alternative diagnoses like myelomatosis, lymphoma, HIV and SLE. A positive M-component in her blood followed by a bone marrow biopsy revealed the presence of hematological disease in the form of MGUS. She has not suffered any serious bacterial infections after starting treatment with IVIG. Despite her age of 69 years she is still working part-time as a nurse and is healthy in all other aspects and physical active. This case report emphasis that clinicians encountering unusual infectious disease entities or unusual frequencies of infectious diseases in the same patient, should be alert regarding the possibility of underlying undiagnosed disease and immune deficiencies. Patients should be evaluated thoroughly for these risk factors regarding potential future life threatening infections in the individual patient. Identifying underlying diagnoses and immune deficiencies gives the possibility for clinical action both regarding prophylactic measures, treatment of underlying disease, treatment of underlying immune deficiencies and early rapid diagnoses of future severe infections.

Table 2. Levels of immunoglobulins and subclasses.

<table>
<thead>
<tr>
<th>Immunoglobulin, g/L (reference values)</th>
<th>April 2014a</th>
<th>September 2014b</th>
<th>November 2014c</th>
<th>May 2015d</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG total (6.4-13.5)</td>
<td>25.4</td>
<td>22.2</td>
<td>&lt;0.1</td>
<td>29.1</td>
</tr>
<tr>
<td>IgA total (0.7-3.12)</td>
<td>0.56</td>
<td>0.41</td>
<td>&lt;0.25</td>
<td>0.35</td>
</tr>
<tr>
<td>IgM total (0.56-3.52)</td>
<td>1.46</td>
<td>1.28</td>
<td>&lt;0.20</td>
<td>1.36</td>
</tr>
<tr>
<td>IgG1 (2.8-8)</td>
<td>22.4</td>
<td>22.6</td>
<td>23.2</td>
<td>23.4</td>
</tr>
<tr>
<td>IgG2 (1.2-5.7)</td>
<td>0.24</td>
<td>0.25</td>
<td>0.21</td>
<td>0.15</td>
</tr>
<tr>
<td>IgG3 (0.24-1.25)</td>
<td>0.150</td>
<td>0.127</td>
<td>0.089</td>
<td>0.089</td>
</tr>
<tr>
<td>IgG4 (0.052-1.25)</td>
<td>0.267</td>
<td>0.254</td>
<td>0.234</td>
<td>0.263</td>
</tr>
</tbody>
</table>

*aEight months after pneumococcal spondylodiscitis; †13 months after pneumococcal spondylodiscitis; ‡sampled on the 5th day of admission with pneumococcal pneumonia with septic shock; §7 months after pneumococcal pneumonia with septic shock.*
References


