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A Case of Community-Acquired Pneumococcal Meningitis Following Acute Sinusitis and Unsuccessful Former Antimicrobial Therapy

Akut Sinüzit ve Başarısız Antimikrobiyal Tedavi Sonrası Gelişen Toplum Kökenli Pnömokokal Menenjit Olgusu

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Abstract

Rapid diagnosis and treatment are critical for patient recovery in bacterial meningitis. Delayed initiation of antibiotic therapy is associated with increased in-hospital mortality and an unfavorable outcome at discharge. We report a 31-year-old female patient presenting with a history of acute sinusitis and cefuroxime medication for 7 days. On the 7th day, the patient was admitted to the emergency department with nausea, vomiting, confusion, headache, tendency to sleep. On physical examination, the patient presented with unresponsiveness and weak neck stiffness as a sign of meningeal irritation. Cerebrospinal fluid (CSF) analysis revealed 13,446 leukocytes per mm^3 with 95% neutrophils and 5% lymphocytes. CSF biochemical analysis indicated low CSF glucose (<1 mg/dL glucose), elevated CSF protein (476 mg/dL total protein) and >2000,00 mg/L albumin. CSF RT-qPCR was positive for *Streptococcus pneumoniae*. The patient was immediately administered ceftriaxone and vancomycin, and recovered without any neurological sequelae. This study highlights the importance of patient follow-up, accurate prognosis and rapid laboratory testing in patients with failed sinusitis treatment.

Keywords *Streptococcus pneumoniae*, meningitis, sinusitis, treatment failure, rapid molecular diagnosis

Özet

Bakteriyel menenjitte hızlı tanı ve tedavi hastanın iyileşmesi için kritik öneme sahiptir. Antibiyotik tedavisine geç başlanması, hastane içi mortalitede artış ve taburcuda olumsuz bir sonuç ile ilişkilidir. Bu yazıda akut sinüzit öyküsü olan ve 7 gün sefuroksim tedavisi almış 31 yaşında kadın bir olgu sunuldu. Hasta 7. gününde bulantı, kusma, bilinç bulanıklığı, baş ağrısı, uykuya eğilim şikayetleri ile acil servise başvurdu. Fiziki muayenede, meningeal iritasyon belirtisi olarak zayıf boyun sertliği gozlendi. Beyin omurilik sıvısı (BOS) analizinde, %95 nötrofil ve %5 lenfosit olmak üzere 13,446/mm^3 lökosit görüldü. BOS biyokimyasal analizde, düşük BOS glikozu (<1 mg/dL glikoz), yüksek BOS proteini (476 mg/dL toplam protein) ve >2000,00 mg/L albümin saptandı. BOS RT-qPCR Streptococcus pneumoniae açısından pozitif olarak sonuçlandı. Seftriakson ve vankomisin tedavisi başlandı ve hasta herhangi bir nörolojik komplikasyon olmadan iyileşti. Bu çalışma tedavi edilemeyen akut sinüzit sonrası gelişen toplum kökenli pnömokokal menenjit vakasını rapor etmekte ve bu vakalarda hasta takibinin, doğru prognozun ve hızlı laboratuvar testlerinin önemini vurgulamaktadır.

Anahtar Kelimeler *Streptococcus pneumoniae, menenjit, sinüzit, başarısız tedavi, hızlı moleküler tanı*

INTRODUCTION

Bacterial meningitis is an infection of the meninges, which is the protective membrane covering the brain and spinal cord, resulting in inflammation. This inflammation can impair brain function, necessitating immediate hospitalization[1]. Pneumococcal meningitis is a medical emergency. Rapid diagnosis and urgent antimicrobial therapy are critical for patient recovery. Delayed initiation of antibiotic therapy is often associated with increased in-hospital mortality and an unfavorable outcome at discharge.

Neisseria meningitidis and *Streptococcus pneumoniae* are the most common causes of community-acquired bacterial meningitis, accounting for 70-75% of the cases. Invasive disease by these pathogens is preceded by nasopharyngeal colonization, after which the bacteria are able to pass the mucosal barrier, invade the bloodstream and eventually cross the blood-brain barrier to cause meningitis. In a subset of patients, the bacteria enter the central nervous system through infected mastoid or paranasal sinuses[2]. Age represents an important risk factor for the development of bacterial meningitis with neonates and older adults having the highest risk. One of the most important predictors of an unfavorable outcome in this disease is advanced age.

In developed countries, the estimated incidence of bacterial meningitis is 2.6-6.0 cases per 100,000 people per year, although it can be up to ten times higher in less developed countries. The mortality rate in high-income countries is approximately 20%, and neurological sequelae occur in almost half of the surviving patients[3]. Recurrent episodes of bacterial meningitis have been described in 5% of community-acquired bacterial meningitis cases, and have been associated with a relatively favorable prognosis. Several factors have been identified that predispose individuals to recurrent meningitis, such as cerebrospinal fluid (CSF) leakage, remote head injury, and an immunocompromised state[4].

Meningitis is often not an isolated infection of the central nervous system, and concomitant bacteremia, pneumonia, or endocarditis are frequently described. Several risk factors and predisposing conditions have been identified which increase susceptibility for bacterial meningitis. These risk factors include medical conditions resulting in immunodeficiency, host genetic factors or anatomical defects of the natural barriers of the central nervous system. In pneumococcal meningitis, increased susceptibility is observed in individuals with underlying conditions such as splenectomy or asplenic states and in children with cochlear implants. The use of immunosuppressive drugs, the presence of diabetes mellitus, a history of splenectomy, infection with human immunodeficiency virus (HIV) or alcoholism is described in 20% of adults with pneumococcal meningitis. In terms of anatomical defects, the disruption of the blood-brain barrier following trauma, surgery, congenital defects or ear and sinus infection can provide an entry for bacterial pathogens into the central nervous system, and therefore are considered as risk factors for meningitis[5]. Combination therapy with vancomycin and a third-generation cephalosporin (either ceftriaxone or cefotaxime) has emerged as the gold standard for antimicrobial therapy as the frequency of penicillin-resistant pneumococci has increased globally[6].

Cerebrospinal fluid Gram-staining enables rapid inspection of the pathogenic bacterium. Bacterial antigen tests have low sensitivity, although they may be useful in individuals with symptoms of bacterial meningitis and negative CSF Gram-staining and culture. In the diagnosis of patients with negative CSF cultures, new molecular approaches for the identification of bacteria in the CSF by polymerase chain reaction (PCR) have emerged as a powerful diagnostic tool with high sensitivity and specificity.

Increased in-hospital mortality and a poor outcome at release are associated to delayed administration of antibiotic treatment for bacterial meningitis. The most prevalent causes of delay include the need for cranial imaging prior to diagnostic lumbar puncture and patient transfers to dif-

ferent hospitals. Therapy is recommended to start before the patient is referred for neuroimaging if imaging will be performed prior to lumbar puncture. Therapy is required to begin immediately following lumbar puncture in patients who have not undergone previous imaging and in whom disease progression is visible, as well as in all patients with turbid CSF, indicative of bacterial meningitis. CSF findings are critical in the differential diagnosis of patients with suspected meningitis.

In the current study, we report a 31-year-old woman presenting with pneumococcal meningitis and a history of acute sinusitis with treatment failure. Microbiological, biochemical and molecular investigation of patient's CSF confirmed the diagnosis of meningococcal meningitis. Written informed consent was obtained from the patient for the publication of this case report.

CASE PRESENTATION

A 31-year-old female patient presented to our emergency department with nausea, vomiting, confusion, headache, and a tendency to sleep. The patient had a medical history of sinusitis. She was administered cefuroxime as an outpatient at a different clinic for 9 days. On the 7th day, the patient condition started to deteriorate and was admitted to the emergency department with the above-mentioned symptoms. On physical examination, she presented with weak neck stiffness as a sign of meningeal irritation and difficulty in cooperation. Kernig's sign and Brudzinski's sign were negative. Patient's eyes were spontaneously closed. She was able to open her eyes in response to speech and could communicate with a few words. She performed one stage motor commands bilaterally. Pupils were reactive to light stimulus, eyes were in midline position. Plantar responses were flexor bilaterally. The patient was admitted to the intensive care unit. An immediate lumbar puncture was performed. The CFS had a cloudy appearance. The CSF sample was simultaneously analyzed for cell type, cell counting, biochemical characterization, bacterial culture, and Gram-staining as well as Qiastat-Dx Meningitis/Encephalitis RT-qPCR Panel using molecular methods. Laboratory investigation of the initial CSF analysis revealed an elevated leukocyte count of 13,446 leukocytes per mm^3 (normal 4–10 $\times 10^3$ leukocytes per mm^3) with 95% neutrophil and 5% lymphocytes, indicative of pleocytosis. CSF biochemical analysis indicated low CSF glucose (<1 mg/dL glucose), elevated CSF protein (476 mg/dL total protein) and >2000,00 mg/L albumin (Table 1).

Table 1. Biochemical analysis of the patient's cerebrospinal fluid

Glucose level, mg\dL	**<1 mg\dL** Normal range (40 - 70)
Total protein, mg\dL	**476 mg\dL** Normal range (15 - 45)
Albumin, mg\L	**>2000,00 mg\L** Normal range (150,00 - 400,00)
Sodium, mmol\L	**138 mmol\L** Normal range (142 - 150)
Potassium, mmol\L	**2.8 mmol\L** Normal range (2,2 - 3,3)
Chloride, mmol\L	**118 mmol\L** Normal range (118 - 132)

All the serum electrolyte and blood glucose levels were normal. Patient CRP level was 2,02 mg/dL upon admission, which peaked up to 16,56 mg/dL post 2 days of diagnosis. An immediate Gram staining of the patient's CSF sample indicated Gram-positive diplococci and multiple polymorphonuclear leukocytes as shown in Figure 1.

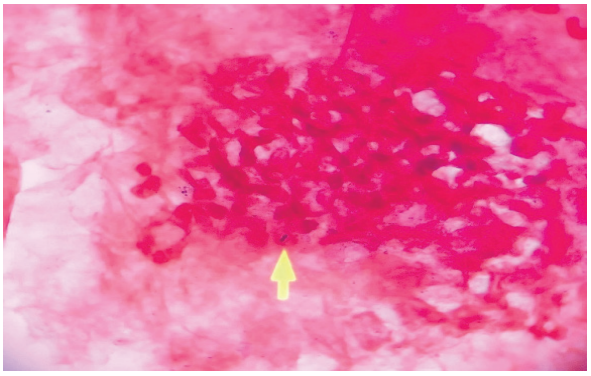

Figure 1. Gram stain of the patient's cerebrospinal fluid indicating the presence of Streptococcus pneumoniae, Gram-positive diplococci as shown by the arrow in direct microscopic examination (x100 magnification)

The RT-qPCR was positive for *Streptococcus pneumoniae* with a cycle threshold (Ct) value of 23.4 as demonstrated in Figure 2. Blood cultures of the CSF were performed. The initial blood culture was positive for *Streptococcus pneumoniae*.

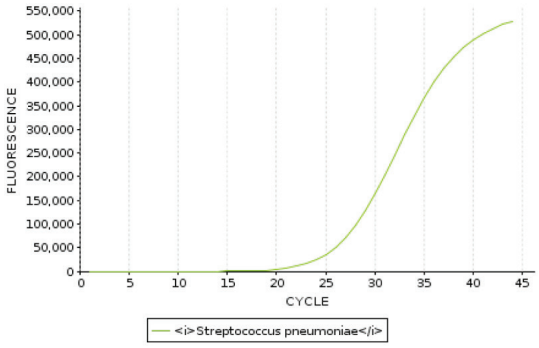

Figure 2. RT-qPCR amplification indicative of the presence of Streptococcus pneumoniae in patient CSF sample

The patient was consequently diagnosed with pneumococcal meningitis. Ceftriaxone was administered with 2x2 g intravenously on the first day and 2x1 g in the following days. Simultaneous intravenous vancomycin was added to the treatment as 2x1 g. Treatment with this combination was completed in 14 days. The patient was transferred and followed-up in the Infectious Diseases Service after two days of administration of antimicrobial therapy. The patient recovered without any neurological sequelae and was successfully discharged within two weeks. The patient received pneumococcal conjugate vaccine after full recovery.

DISCUSSION

Streptococcus pneumoniae is the most common cause of acute bacterial meningitis in adults, and case-fatality rates for high-risk patients have been reported to be as high as 55% even in the presence of appropriate antimicrobial therapy[7]. Pneumococcal meningitis is in most cases secondary to a primary infection focus such as ears (30%), lungs (18%), sinuses (8%), while no primary infection focus was found in 42% of the cases[8]. The most common symptoms of *S. pneumoniae* meningitis include fever, headache, and vomiting, accompanied by comma, neck rigidity, and positive Kernig's and Babinski signs.

The majority of patients with bacterial meningitis have a CSF total leukocyte count of greater than 100 x 10^6/L. A glucose level in the CSF lower than 40% of the serum glucose level shows an 80% sensitivity for the diagnosis of bacterial meningitis[9]. Adults rarely have bacterial meningitis with initially normal CSF, but children are more prone to experience this condition. The lumbar puncture is performed shortly after the onset of the initial clinical symptoms and may result in an initial normal sample, but other circumstances, such as concurrent use of antibiotics, may also be play a role in this phenomenon.

When contamination can be successfully ruled out, a positive CSF culture is the gold standard for the diagnosis of bacterial meningitis. Besides, a positive Gram stain can aid in diagnosis. Recent advancements in PCR-based technologies for the identification of bacterial meningitis provide a rapid alternative diagnostic method, particularly for cases in which CSF samples are culture-negative.

In the current study, we are presenting a case of pneumococcal meningitis in a 31-year-old female patient with an initial prognosis of acute sinusitis and unsuccessful former antimicrobial therapy, which resulted in delayed treatment with appropriate antibiotics. Such delay could have had a potentially fatal outcome. Typical findings of bacterial meningitis including low glucose levels, elevated protein levels, and >2000,00 mg/L albumin were detected in patient CSF sample. Patient CRP levels were 2,02 mg/dL upon admission, which peaked up to 16,56 mg/dL post 2 days. Gram staining indicated Gram positive diplococci in CSF, and the RT-qPCR was positive for *S. pneumoniae* with a cycle threshold (Ct) value of 23.4. Third-generation cephalosporins are the choice of therapy for *S. pneumoniae* meningitis. The patient was immediately administered ceftriaxone and vancomycin. The patient recovered without any neurological sequelae and was successfully discharged

within two weeks.

In a study involving a patient with documented meningitis, Montassier and colleagues reported a 60-year-old woman presenting with fever and headache. Her medical history included an appendectomy and a hysterectomy. She was not taking any antibiotic therapy and was not vaccinated against pneumococcus. The night before patient visit to the hospital, she had a fever of 38.7°C, a frontal headache and neck pain. Laboratory investigations revealed an elevated serum leukocyte count of 16.6 (normal 4–10) $\times 10^6$ /L. The patient's CSF was clear and analysis showed a protein level of 0.39 g/L, a glucose level of 3.9 mmol/L (the serum glucose level was 6.1 mmol/L) and a leukocyte count of less than 1×10^6 /L. A Gram stain of the patient's cerebrospinal fluid showed no microorganisms. Bacterial meningitis was diagnosed with a four-day delay after the initial clinical symptoms. The patient responded favorably to treatment with intravenous ceftriaxone. In a separate study, authors reported 20 cases of bacterial meningitis confirmed by blood culture while patients had initial negative culture of CSF, resulting in delayed antibiotic therapy[10].

In a study aiming to define risk factors predisposing to community-acquired bacterial meningitis (CBM), 40 out of 201 cases (20%) of CBM were reported to have otitis media or acute and chronic sinusitis 1-5 weeks before the onset of meningitis[11]. Being a well-known risk factor bacterial meningitis, conditions such as sinusitis should be carefully treated and outpatients should be followed up to ensure the completion of antimicrobial therapy to prevent serious future complications.

CONCLUSIONS

In patients with a failed former therapy for sinusitis or otitis media, bacterial meningitis is a serious complication which should always be considered by the clinicians. In such cases in which patients have received former suppressive therapy, molecular diagnostic methods represent a critical tool for the rapid detection of the causative agent in CSF and initiation of appropriate antimicrobial therapy.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authorship Contributions

Concept: B.B, Design: B.B., K.S., Data Collection or Processing: B.B., M.M.Y.A., Analysis or Interpretation: B.B, M.M.Y.A., N.D., K.S., Literature Search: B.B., M.M.Y.A., Writing: B.B., M.M.Y.A, K.S., N.D.

Ethical Approval

Due to the nature of this retrospective study and the preserved anonymity of the patient, a waiver of ethics committee approval was obtained from Near East University. All methods were carried out in accordance with the guidelines and regulations of Declaration of Helsinki.

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Informed Consent

Written informed consent was obtained from the patient for the publication of this case report.

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