

## Short Communication

### Infected Subdural Hematoma in an Infant

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**SUMMARY:** We report the case of a 1-year-old boy with an infected subdural hematoma due to *Streptococcus pneumoniae* identified by latex agglutination test and polymerase chain reaction amplification of a bacteria-specific gene. The present case demonstrated the need to include infected subdural hematoma in the differential diagnosis of suspected subdural empyema, and suggested the usefulness of combining these methods to identify a causative organism.

Subdural empyema has been estimated to account for 10–20% of all childhood intracranial bacterial infections, and it usually develops as a complication of bacterial meningitis (1). However, a few reports have described infected subdural hematoma resulting from hematogenous infection of a pre-existing chronic subdural hematoma in children (2–7). It is difficult to identify the causative agents of deep-seated bacterial infections, including subdural hematoma, due to treatment with antibiotics prior to surgical interventions. We report an infant case of infected subdural hematoma caused by hematogenous *Streptococcus pneumoniae* infection of a preexisting asymptomatic chronic subdural hematoma. The pathogen was identified by latex agglutination test and polymerase chain reaction (PCR) amplification of the *lytA* gene, a bacteria-specific gene of *S. pneumoniae*.

A 1-year-old boy was admitted to our hospital for evaluation and treatment of a subdural effusion. Five days before admission, the patient had developed a high fever without specific symptoms. On the next day (the 2nd day of illness), he had been admitted to another hospital due to persisting high fever and convulsions, and had regained normal consciousness shortly after admission. The peripheral blood sample showed a leukocyte count of 24,100/ $\mu$ l, with 64.4% neutrophils, and a serum C-reactive protein (CRP) level of 29.53 mg/dl. Cerebrospinal fluid (CSF) analysis revealed a cell count of 43/ $\mu$ l with 56% polymorphonuclear leukocytes and normal CSF glucose and protein levels. Although bacterial meningitis was suspected, both the CSF and blood microbial cultures were negative. The high fever continued, despite the administration of intravenous antibiotics, ampicillin and cefotaxime (200 mg/kg/day in 4 divided doses, respectively). Computed tomography (CT) of the head on the 5th day of illness revealed fluid collection in the right frontal subdural space, with a midline shift. The patient was transferred to our hospital on the 6th day of illness with suspected subdural empyema. The patient's past medical history was unremarkable, except for habitual head-pounding against the wall and floor. An elder brother had died unexpectedly at 1 year of age;

however, no details about the case were available.

On admission, the patient's temperature was 38.6°C. The palpebral conjunctiva was pale, and expiratory wheeze was heard upon auscultation. No symptoms of acute otitis media and no traumatic injuries (e.g., purpura and bruising) were observed. The patient was conscious and alert, and neurological examination revealed no additional abnormalities. The peripheral blood count revealed a leukocyte count of 12,900/ $\mu$ l, with 22.5 % neutrophils, a hemoglobin concentration of 7.7 g/dl, and a platelet count of  $430 \times 10^3/\mu$ l. The serum CRP level was 20.92 mg/dl. CSF analysis revealed a lymphocyte-predominant cell count of 17  $\mu$ l. Although the bacterial culture of a sample obtained by nasal swab yielded *S. pneumoniae*, the CSF and blood bacterial cultures were negative. Magnetic resonance imaging disclosed a lesion in the right frontal region with a mass effect, which showed a low signal and a high signal on the T<sub>1</sub>-weighted and T<sub>2</sub>-weighted images, respectively. T<sub>1</sub>-weighted imaging was enhanced with gadolinium-diethylenetriaminepenta-acetic acid, and disclosed a loculated collection of fluid surrounded by a rim-enhancing area (Fig. 1). After the patient's admission, an emergency aspiration was performed via a single burr hole, as a subdural empyema with a mass effect was suspected (Fig. 2). The aspiration yielded 15 ml of bloody fluid containing leukocytes with a neutrophil predominance and no clotting. The aspirated samples was subjected to Gram staining and bacterial culture, as well as latex agglutination

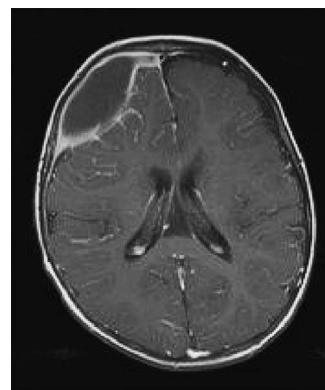


Fig. 1. T<sub>1</sub> weighted magnetic resonance imaging (MRI) with gadolinium enhancement before first operation.

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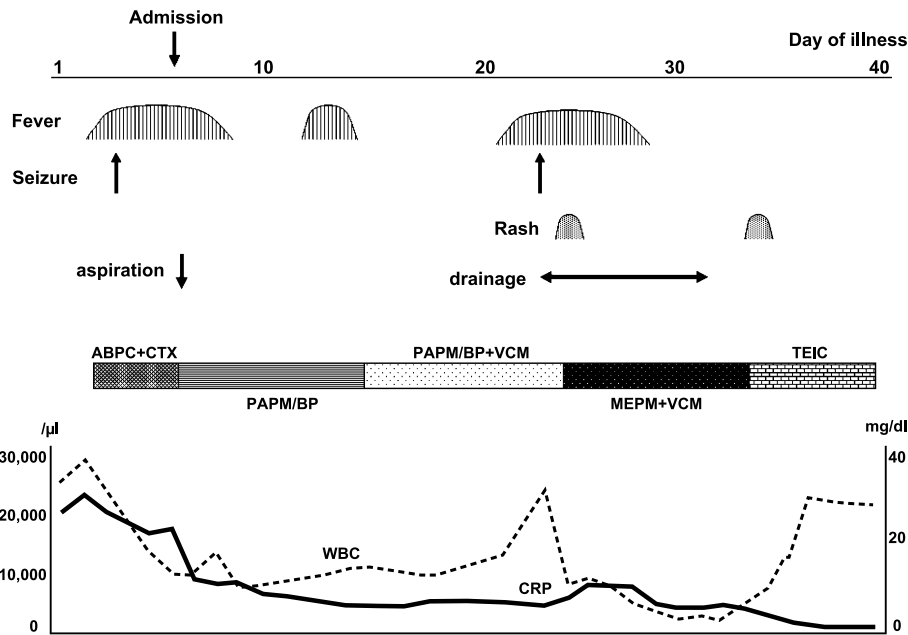


Fig. 2. Clinical course and serial laboratory data. ABPC, ampicillin; CTX, cefotaxime; PAM/BP, panipenem/betamipron; VCM, vancomycin; MEPM, meropenem; TEIC, teicoplanin.

test for *S. pneumoniae* (Slidex-Meningite-Kit 5; bioMerieux, Marcy l'Etoile, France) and PCR amplification of *lytA* gene, which is highly specific for *S. pneumoniae*. The fluid was centrifuged once, and the supernatant was used for the latex agglutination test. We also extracted and purified DNA from specimens using a GenomicPrep Cells and Tissue DNA Isolation Kit (GE Healthcare UK Ltd., Buckinghamshire, UK) in accordance with the manufacturer's instructions. The sequences of *lytA* primers used for the PCR were as follows: 5'-CAACCGTACAGAATGAAGCGG-3' and 5'-TTATTCG TGCAATACTCGTGCG-3' (8,9). The length of the PCR product was 319 bp. The PCR mixture (25  $\mu$ l) contained 0.2 mM concentrations of each deoxyribonucleoside triphosphate, 10 mM Tris-HCl buffer, 50 mM KCl, 2 mM MgCl<sub>2</sub>, 2.5 U of *Ex Taq* polymerase (TaKaRa-Bio Inc., Shiga, Japan), a 0.5- $\mu$ M concentration of each primer, and 1  $\mu$ l of template DNA. The PCR protocol was 35 cycles of 94°C for 1 min, 55°C for 1 min, and 72°C for 1 min. PCR products were electrophoresed in 1.5% agarose gel and stained with ethidium bromide. The lower limit of detection,  $1 \times 10^4$ /ml, was assessed by PCR reaction on serial 10-fold dilutions of purified DNA from a clinically isolated *S. pneumoniae* strain. Although both the Gram stain and bacterial culture of the fluid were negative, both the latex agglutination test and PCR amplification of the *lytA* gene were positive (Fig. 3). Neither the *S. pneumoniae* antigen nor the *lytA* gene was detected in the CSF obtained before the first dose of antibiotics on the 2nd day of illness. The same samples were negative for *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Escherichia coli* K1, and group B streptococcus antigens, as determined by use of the Slidex-Meningite-Kit 5. Based on these findings, we diagnosed this patient as having *S. pneumoniae* infection in the subdural space. After surgical intervention, a head CT study revealed a decrease in the amount of right frontal subdural effusion. However, the patient's temperature remained high, despite the sequential administration of several intravenous antibiotics (panipenem/betamipron 120 mg/kg/day in 4 divided doses, panipenem/betamipron plus vancomycin 60 mg/kg/day in 4 divided doses), and the patient had a second

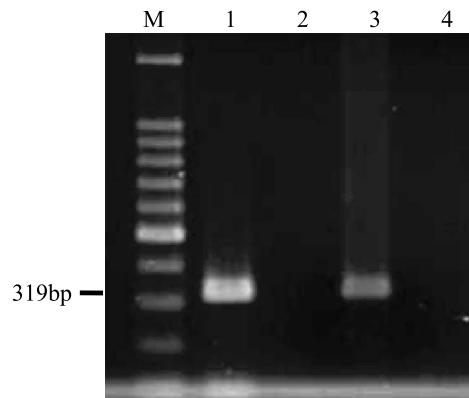


Fig. 3. Detection of *lytA* gene (319-bp product) by RT-PCR. Lane 1, positive control; lane 2, negative control; lane 3, patient sample (subdural effusion: on the 6th day of illness); lane 4, patient sample (cerebrospinal fluid: on the 2nd day of illness).

convulsive attack on the 23rd day of illness (Fig. 2). Head CT showed a renewed increase in the amount of right frontal subdural effusion. A second aspiration of fluid via a single burr hole and drainage were performed on the same day. After drainage had been initiated, the patient showed a gradual defervescence, during which time antibiotic treatment (vancomycin plus meropenem and teicoplanin) had to be switched twice due to suspected drug eruption. The drainage tube was removed 7 days later, and the amount of subdural effusion did not increase thereafter. The patient recovered without sequelae and was discharged.

In young children, subdural empyema usually develops as a complication of bacterial meningitis, whereas in older children and adults it is related to paranasal sinusitis and middle-ear infections (1,5). In addition, subdural empyema is also associated with craniotomy and post-operative infection at any age (1). In the present case, instead of associating the empyema with hemorrhage, we speculated that a hematogenous pneumococcal infection of the hematoma had given rise to the empyema, primarily due to the absence of common

predisposing factors for subdural empyema (e.g., bacterial meningitis, paranasal sinusitis, and craniotomy). The presence of prior chronic subdural hematoma was suspected, as the patient habitually had pounded his head against walls and floors. Although this habit is unusual, both the patient's development and growth were within normal range. To our knowledge, there have been only six reports of infected subdural hematoma in children (2-7). These previously reported cases, taken together with the present case indicate the need to include infected subdural hematoma in the differential diagnosis of suspected subdural empyema. The prolonged clinical course can at least in part be explained by the low level of penetration of antibiotics into the lesion. In such situations, aggressive surgical drainage at an early stage of disease, concomitant with long-term administration of antibiotics, would be necessary. In addition, it is possible that the causative agent in our case might have been highly resistant to antibiotics.

The diagnosis of pneumococcal central nervous system infection is primarily based on the results obtained from Gram staining and bacterial cultures of clinical specimens. However, the positive rates associated with these methods in pediatric cases with bacterial meningitis are 57 and 53%, respectively (10). Moreover, in cases with prior use of antibiotics, these rates are much lower. Latex agglutination test for the detection of bacterial antigens and PCR amplification of bacterial genes would be useful for diagnosing cases with negative smears and cultures, especially in pretreated cases. Slidex-Meningite-Kit 5, a latex agglutination test for five common pathogens of bacterial meningitis, is capable of detecting pneumococcal exoantigens in body fluids at a detection level of 100 ng/ml. Camargos et al. reported that the sensitivity and the specificity of this antigen detection kit were 86.5 and 100% for *S. pneumoniae*, respectively (11). The *lytA* gene encodes autolysin and is highly specific to *S. pneumoniae*. Detection of the *lytA* gene by PCR amplification is useful for the identification of *S. pneumoniae* without cross-detection of other streptococci (12). PCR amplification of the 16S ribosomal RNA gene using universal primers with subsequent sequencing followed by phylogenetic analysis is an alternative sensitive molecular technique for the detection and identification of bacteria in smear- or culture-negative clinical specimens (13). However, in this system, any attempt to increase sensitivity by increasing the number of amplification cycles is usually hampered by the detection of minimal

amounts of bacterial contaminants present in the environment. In contrast, PCR detection of the *lytA* gene is an advantageous in that sensitivity can be increased by increasing the number of amplification cycles without the interference of contaminating environmental bacteria. In deep-seated bacterial infections, antibiotic treatment usually precedes a surgical procedure, rendering the identification of a causative agent difficult. The combination of latex agglutination testing and PCR amplification of bacteria-specific genes would be useful for the identification of causative organisms in cases of deep-seated bacterial infection.

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