

DEVELOPMENT OF PURULENT MENINGITIS IN A CHILD WITH NEPHROTIC SYNDROME WHILE RECEIVING CEPHTRIAZONE PLUS AMIKACIN

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A child with nephrotic syndrome (NS) presented with peritonitis caused by *E. coli* susceptible to both cephtriazone and amikacin. Purulent meningitis developed in accompanying with clinical and laboratory findings at the 5th day of treatment. Pneumococcal antigen was detected in cerebro-spinal fluid and meningitis was treated with meropenem. Development of pneumococcal meningitis while receiving broad-spectrum antibiotics for peritonitis is an unusual situation.

Key words: Children, nephrotic syndrome, meningitis, peritonitis, meropenem

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INTRODUCTION

Bacterial infections are frequent in nephrotic children. The most common infection is peritonitis, often with *S. pneumoniae*. Children with nephrotic syndrome may also develop cellulitis, pneumonia or meningitis. Several factors may explain the tendency of nephrotic children to develop bacterial infections: low IgG levels due to impaired synthesis or urinary loss, urinary loss of Factor B and impaired cellular immunity (1, 2).

We presented this patient due to uniqueness of the meningitis development while under broad spectrum antibiotic coverage.

CASE

An 8 year-old boy presented with a 4-year history of nephrotic syndrome (NS) was hospitalized for treatment of peritonitis and new relapse. During his four years follow-up period, he had three relapses of NS occurring once a year. After six months from the cessation of last steroid treatment, he was referred to our hospital with symptoms and findings of fever, severe extensive edema, abdominal distention and direct tenderness to palpation. Throughout the last 6 months of follow up period, he did not receive corticosteroids and did not have proteinuria. Formerly, he had infectious episodes of two

tonsillitis, three peritonitis, gastroenteritis, and mumps at different times. Each peritonitis attacks had been together with the relapses.

Three days before the last hospital admission, he was given medication for an upper respiratory tract infection. Although no pathogenic microorganism was grown in the throat culture, we had started oral penicillin (Penicillin V 50.000 U/kg/day, tid) before obtaining culture result at the outpatient clinic. At the fourth day of penicillin treatment he was admitted to our emergency department with complaints of abdominal discomfort, vomiting and frequent breathing. Physical examination revealed weakness and pale appearance, heart rate 96/min, respiratory rate 24/min, and blood pressure 100/60 mm Hg. Respiratory sounds were decreased at the right basal pulmonary area, abdominal examination revealed tenderness to palpation and rebound tenderness, auscultation revealed hypoactive bowel sounds. There was a pretibial edema with (+++) godet formation. Laboratory investigations: Urinalysis showed a specific gravity of 1030, pH 6.5, proteinuria 500 mg/dl, 10-12 leukocytes per high power field with leukocyte cylinders in some fields and a sterile culture. Thorax X-ray disclosed infiltration in right pulmonary area; Complete blood count: white blood count 19.600/mm³, hemoglobin 14 g/dl, hematocrite 42.2%, mean corpuscular volume 83 fl, platelet count 777.000/mm³; Blood smear: Polymorphonuclear leukocytes

80%, stab 16%, lymphocyte 4%, toxic granulation (++)). Peritoneal fluid culture yielded *E. coli*. C-reactive protein (+++), erythrocyte sedimentation rate 82 mm/h, complement factor 3 (C3) 87 mg/dl (N: 70-140), C4 35 mg/dl (N: 16-47). Biochemistry panel including blood glucose, blood urea nitrogen, creatinine, Na⁺, K⁺, Cl⁻, P, total bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, lactate dehydrogenase, creatinine kinase and uric acid were within normal limits, but Ca⁺ (7.5 mg/dl), total protein (4 g/dl), albumin (1.9 g/dl) and total cholesterol (307 mg/dl) were found to be abnormal.

For the treatment of peritonitis, Penicillin G (300.000 U/kg) plus amikacin (15 mg/kg) were started after obtaining blood, urine and peritoneal fluid samples for culture. Blood and urine cultures were sterile but peritoneal fluid culture yielded *E. coli* sensitive to both cephtriaxone and amikacin, so we interchanged penicillin G with cephtriaxone (50 mg/kg/dose, twice daily). At the fifth day of cephtriaxone treatment –eighth day of intravenous antibiotic treatment- while all signs and symptoms of peritonitis subsided, high fever was detected once again together with neck stiffness, positive Kernig and Brudzinsky signs, nausea and vomiting. Meanwhile patient became unconscious. On the other hand, after 3 days of cephtriaxone treatment, no microorganism was grown on the culture of peritoneal fluid and no bacteria were detected by Gram stain. Examination of cerebrospinal fluid (CSF) revealed increased CSF pressure, positive Pandy reaction (+++), abundant white blood cells (80% polymorphonuclear cells) with CSF protein 96 mg/dl, CSF glucose concentration 40 mg/dl (synchronized blood glucose 90 mg/dl), chloride 92 mg/dl. CSF culture was sterile and no microorganism was identified from Gram staining of CSF smear. Rapid diagnostic test with latex agglutination was performed and pneumococcal antigens were detected in CSF. After empirically started meropenem (90 mg/kg/day, tid) fever subsided and clinical findings of meningitis were resolved within 3 days. Meanwhile amikacin was stopped. Laboratory finding of CSF normalized at the 3rd day of meropenem treatment and clinically the patient entirely recovered during subsequent clinical course. After the completion of two weeks of meropenem, oral steroid was started and the patient achieved remission at the 10th day of steroid treatment. After that, the patient remained in remission

for 5 months and following 2.5 months of steroid-free period he developed bacterial peritonitis again. This time, *S. pneumoniae* was isolated from peritoneal fluid culture and peritonitis was found to be resolved by 12 days of cephtriaxone treatment and the patient went into remission once again. Although pneumococcal vaccination was performed to the child after his first peritonitis attack, the patient still developed peritonitis three times. Measurement of IgG concentrations during the remission period between the 2nd and 3rd relapses revealed a normal total immunoglobulin levels with low IgG₂ concentration for the range of the patient's age: total IgG 1227 mg/dl (N: 700-2140), IgA 404 mg/dl (N: 68-332), IgM 126 mg/dl (N: 67-345), IgE:701 IU/ml; IgG subgroups: IgG₁ 1058 mg/dl (N:410-1180), IgG₂ 70 mg/dl (N:80-570), IgG₃ 74 mg/dl (33-184). At the time of last relapse, ultrasonography showed an increased renal parenchymal ecogenicity with otherwise normal appearance. Patient now is in remission for the last 12 months and coming to the routine controls.

DISCUSSION

There is a tendency to development of infections, especially caused by capsulated bacteriae like *S. pneumoniae* and *H. influenzae*, in nephrotic patients due to various risk factors including reduced immunoglobulin concentration via urinary loss of IgG, depletion of properdin factor B, the deleterious effects of edematous tissue resembling culture medium, decreased bactericidal activity of leukocytes by immunosuppressive therapy and inefficient perfusion of spleen due to hypovolemia (1-4). Case history, clinical and laboratory evaluation and 4 year-follow up of our patient disclosed a tendency to development of infections particularly peritonitis. After the remission of second relapse, the patient was vaccinated with pneumococcal vaccine; unfortunately he experienced two additional peritonitis attacks after vaccination. Although total immunoglobulin concentration was in normal limits, IgG₂ concentration was below normal cutoff value. We think low IgG₂ concentration together with pulmonary infection might have resulted in relapse and peritonitis.

Although we could not isolate any microorganism from CSF during the course of meningitis, the etiologic agent of meningitis might have been resistant to both cephtriaxone and amikacin since meningitis had developed

under the treatment of these antibiotics. We think that microorganism leading to bacterial meningitis was not *E. coli* since we had used cephtriaxone according to susceptibility testing results of peritoneal fluid, prior to development of meningitis and latex agglutination for pneumococci was positive. Our patient might have developed meningitis probably by a cephtriaxone-resistant-strain of *S. pneumoniae* arisen from pneumococcal bacteremia of pulmonary infection.

Pneumococcal vaccination did not exert any effect on the following peritonitis attacks. Although we could not measure antibody against pneumococci, there are some reports about insufficiency of vaccination for the prevention of pneumococcal infections in nephrotic patients (2, 5). We treated our patient with meropenem for 14 days, which was reported as a second drug, behind vancomycin for the resistant pneumococcal infections. For the treatment of meningitis, meropenem, a carbapenem-class antibiotic, was demonstrated having increased activity against penicillin-resistant pneumococci, while having a safety profile similar to that of the cephalosporins (6, 7).

In conclusion, meningitis could have occurred while the patient has been treated with broad-spectrum antibiotics and meropenem was found to be effective in our case.

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