Spontaneous *Escherichia coli* Meningitis Associated with Hemophagocytic Lymphohistiocytosis

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Spontaneous *Escherichia coli* meningitis has not been previously reported in association with hemophagocytic lymphohistiocytosis (HLH). A previously healthy 72-year-old woman was admitted due to fever, nuchal rigidity, disturbed consciousness and splenomegaly. Anemia, thrombocytopenia and hyperferritinemia developed on the 8th day of hospitalization. Cultures of cerebrospinal fluid and blood grew *E. coli*. Abundant macrophages overwhelmed erythrocytes in the bone marrow aspirate, confirming the presence of hemophagocytosis. *E. coli* meningitis was managed with a 40-day course of antibiotic treatment. However, the severity of anemia and thrombocytopenia progressed despite intensive transfusion therapy. The patient died of HLH on the 60th day of hospitalization. [J Formos Med Assoc 2006;105(9):756–759]

**Key Words**: *Escherichia coli*, hemophagocytosis, meningitis

*Escherichia coli* meningitis is rare in adults and generally occurs following head trauma or neurosurgical treatments.† Spontaneous *E. coli* meningitis is extraordinarily rare. The complications of *E. coli* meningitis encompass septic shock, disseminated intravascular coagulopathy, stroke and hydrocephalus.‡ Hemophagocytic lymphohistiocytosis (HLH) is known to be associated with several infectious diseases. We report a case of spontaneous *E. coli* meningitis concurrently complicated by HLH.

### Case Report

A previously healthy 72-year-old woman was hospitalized due to fever and disturbed consciousness for 1 day. She had no systemic diseases, such as diabetes mellitus and autoimmune diseases, history of head trauma, alcoholism or major operation. On admission, the patient was drowsy with a body temperature of 39.6°C and a rigid neck. Physical examination showed a palpable spleen in the supine position. The liver was not enlarged. Cervical and inguinal lymph nodes were not palpable. Laboratory findings showed leukocytosis with white blood cell (WBC) count of 23.8 × 10⁹/L (normal, 3.5–11 × 10⁹/L) with 92.5% polymorphonuclear neutrophils. The hemoglobin (Hb) levels and blood platelet count were 92 g/L (normal, 120–160 g/L) and 163 × 10³/μL (normal, 150–400 × 10³/μL), respectively. The C-reactive protein level was 3606 mg/L (normal, <5 mg/L), albumin level was 22 g/L (normal, 35–55 g/L) and alkaline phosphatase level was 120 U/L (normal, 28–94 U/L). The prothrombin time (PT) and

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**Accepted**: October 4, 2005
partial thromboplastin time (PTT) were normal. The serum levels of electrolytes, glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase and total bilirubin were within normal range. Cerebrospinal fluid (CSF) analysis showed a leukocyte count of $5.5 \times 10^3$/L (normal, $< 5 \times 10^3$/L) with 96% neutrophils, raised protein concentration (1.05 g/L; normal, $< 0.45$ g/L) and diminished glucose ($< 0.28$ mmol/L; normal, 2.78–4.44 mmol/L). Both CSF and blood cultures grew *E. coli*.

Intravenous penicillin-G, 24 million UI, and ceftriaxone, 2 g/day, were administered. Eight days after admission, the Hb levels and platelet count decreased to 67 g/L and $76 \times 10^9$/L, respectively. Consequently, serial tests for anemia were arranged. Blood ferritin was elevated at 2917.28 pmol/L (normal, 22.47–653.88 pmol/L). Serum iron levels and total iron binding capacity were normal. Test for Bence–Jones protein in urine was negative. Whole body Tc$^{99m}$ methylene diphosphonate bone scan showed no malignancy. Bone marrow aspirate at 10 days after admission indicated hemophagocytosis (Figure).

Six units of packed red blood cells (pRBC) were transfused between the 9th and 20th day of hospitalization. The Hb level returned to 76 g/L, and the platelet count decreased to $49 \times 10^9$/L. Four units of pRBC and 24 units of platelets were transfused again. The Hb level increased slightly to 85 g/L following transfusion. However, the platelet count further reduced to $35 \times 10^9$/L. PT and PTT remained normal.

Shortness of breath and fever up to 39°C developed 30 days after admission. Chest roentgenography showed right lower lobe pneumonia. Sputum culture grew oxacillin-resistant *Staphylococcus aureus*. The WBC count was $9.1 \times 10^9$/L with 58% polymorphonuclear neutrophils and 6% bands. Penicillin-G was replaced with teicoplanin 400 mg/day. CSF analysis was normal at the end of 40 days of antibiotic treatment. Over the next 20 days, Hb and platelet count decreased to 59 g/L and $10 \times 10^9$/L, respectively, despite continuous blood transfusion (40 units of pRBC and 240 units of platelets in total). The PT and PTT levels remained normal. Massive bleeding of genitourinary, upper and lower gastrointestinal tract developed 55 days after admission. The patient died of severe hypovolemic shock on the 60th day of hospitalization.

**Discussion**

*E. coli* meningitis is common in neonates. It affected less than 1.5% of cases of acute bacterial meningitis in adults. Activity manifestations of meningitis, such as fever, nuchal rigidity and disturbed consciousness, are easily noticed in most patients with *E. coli* meningitis. This patient had acute onset of illness, which was characterized by fever, nuchal rigidity and disturbed consciousness. CSF characteristics including decreased glucose level, elevated protein concentration and pleocytosis with predominant polymorphonuclear cells implied bacterial meningitis. The presence of *E. coli* in both CSF and blood cultures confirmed the diagnosis of *E. coli* meningitis.

Up to 80% of *E. coli* meningitis arise following penetrating procedures or trauma of the skull or the spine. The other 20% of cases, known as spontaneous meningitis, are often community-acquired. Spontaneous *E. coli* meningitis has been reported in patients with chronic liver diseases, chronic alcohol abuse, diabetes mellitus, human

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**Figure.** Results of bone marrow biopsy (hematoxylin & eosin, 400×) show phagocytized mature erythrocytes displacing the nucleus to the edge of the macrophage (arrows). These changes suggest hemophagocytosis.
immunodeficiency virus infection, spinal congenital malformation, malignant diseases, abortion, and urinary tract infection.\textsuperscript{4,6} Most instances of spontaneous \textit{E. coli} meningitis, including the present case, were associated with bacteremia, indicating the hematogenous route of bacterial dispersal.\textsuperscript{2} The mortality rate of adult \textit{E. coli} meningitis continues to be around 40% even in the era of a new generation of antibiotics.\textsuperscript{3} Unfavorable aspects of prognosis for \textit{E. coli} meningitis include nosocomial acquisition, improper antibiotic treatment, presence of bacteremia and shock.\textsuperscript{2,5,7} Complications of \textit{E. coli} meningitis have been reported in 55% of adult patients, comprising hydrocephalus, stroke, cerebral herniation, hearing impairment, septic shock and disseminated intravascular coagulopathy.\textsuperscript{3} In this patient, bacteremia was the sole factor linked with poor response. Nevertheless, HLH, an infrequent complication of bacterial meningitis, developed during the following illness.

Clinical diagnosis of HLH should fulfill five out of the following eight criteria: fever, splenomegaly, cytopenias (affecting more than two of three lineages), hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow, spleen, or lymph nodes, ferritin $> 500$ ng/mL, low or absent NK-cell activity, soluble CD25 $> 2400$ U/mL.\textsuperscript{5} In this patient, hemophagocytosis in the bone marrow, fever, splenomegaly, anemia, thrombocytopenia and hyperferritinemia verified the diagnosis of HLH. Other causes of cytopenia, such as disseminated intravascular coagulopathy, autoimmune diseases and drugs (penicillin-G, ceftirixone), were considered unlikely because of normal PT and PTT, advanced age and continuous deterioration after drug withdrawal.

HLH has been reported to be connected with infection, malignancy, autoimmune diseases and drugs.\textsuperscript{9} Infection-associated HLH is known to be caused by virus, whereas other pathogens, such as \textit{Mycobacteria tuberculosis}, \textit{Streptococcus pneumoniae}, \textit{Staphylococcus aureus}, \textit{Mycoplasma pneumoniae}, Gram-negative bacteria, rickettsiae and fungi, have also been observed.\textsuperscript{10,12} The clinical features of HLH induced by viral infections and those induced by bacterial infections are indistinguishable.\textsuperscript{4,11} In this case, the clinical characteristics of HLH were demonstrated in the early phase of \textit{E. coli} meningitis. Staphylococcal pneumonia developed 20 days after the diagnosis of HLH. Hence, \textit{E. coli} meningitis was considered the most likely possible infection provoking HLH. Only five cases of \textit{E. coli} infection associated with HLH have been reported so far, and all five had either urosepsis or pneumonia.\textsuperscript{10,11,13} Meningitis-associated HLH has been rarely reported, and \textit{E. coli} meningitis-associated hemophagocytic syndrome remains unreported.

Pathologic features of HLH include proliferation of benign histiocytes with marked hemophagocytosis in the bone marrow, spleen or lymph nodes. The pathogenesis of infection-associated HLH remains unclear. Whether HLH associated with viral infection and bacterial infection shares similar pathogenesis also remains unclear.\textsuperscript{4,11} Augmented cytokines such as IFN-$\gamma$, TNF-$\alpha$ and IL-6 may exert a major influence on hemophagocytosis.\textsuperscript{14} Recently, some mutations associated with HLH were identified in genes involved in the granule exocytosis pathway (e.g. \textit{PRF1}, \textit{UNC13D}, \textit{RAB27A}, \textit{SH2D1A}, \textit{CHS1}), which controls immune responses to infection.\textsuperscript{15–18} This patient may have been a carrier of such genetic mutations, which can raise the susceptibility to HLH after infections.

The only successful treatment of HLH is treating the underlying infection. Blood transfusion may be the most significant supportive therapy during the acute illness.\textsuperscript{19} The effects of steroid, intravenous immunoglobulin, plasmapheresis and immunosuppressants remain controversial.\textsuperscript{20–22} Despite appropriate treatment, the mortality rate of HLH is as high as 38.5%.\textsuperscript{23} Negative prognostic factors include age > 30 years, worsening anemia and thrombocytopenia, absence of lymphadenopathy, raised alkaline phosphatase and total bilirubin levels, presence of disseminated intravascular coagulopathy and hyperferritinemia.\textsuperscript{24} In this patient, aspects linked to a poor outcome included old age, deteriorating anemia, thrombocytopenia and hyperferritinemia.
Subsequent development of nosocomial pneumonia might trigger hypercytokinemia and thereby aggravate hemophagocytosis. These clinical developments led to the poor outcome in this patient.

In conclusion, our review of the literature found no previously reported cases of HLH associated with spontaneous *E. coli* meningitis. While bacterial meningitis was successfully treated by antibiotics, this patient died due to reactive hemophagocytosis. Invasion of the blood brain barrier by *E. coli* may have led to the spontaneous *E. coli* meningitis. Unidentified mutations related to the granule exocytosis pathway may have contributed to this case of infection-associated HLH.

References