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Case Report

쯔쯔가무시 뇌막염과 연관된 이크론성 감마글로불린병증

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Transient Biclonal Gammopathy Associated With Tsutsugamushi Meningitis

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Biclonal gammopathy is characterized by the presence of two different monoclonal immunoglobulins, and the clinical findings of biclonal gammopathy are similar to those of monoclonal gammopathy. An association between biclonal gammopathy and tsutsugamushi meningitis has not been reported previously. Here, we report a case of a 55-year-old man presented with fever and decreased mentality. A cerebrospinal fluid (CSF) test and an indirect immunofluorescent antibody test for *Orientia tsutsugamushi* revealed tsutsugamushi meningitis. CSF and serum immunofixation electrophoresis revealed biclonal gammopathy (IgG-κ, IgG-λ). His symptoms improved after antibiotics treatment, and serum biclonal gammopathy completely disappeared.

Key Words: *Orientia tsutsugamushi*, Meningitis, Biclonal gammopathy

Scrub typhus is an acute febrile illness caused by *Orientia* (formerly *Rickettsia*) *tsutsugamushi*, an arthropod-borne obligate intracellular gram-negative organism that targets vascular endothelial cells.[1-4] Neurological complications of scrub typhus are reported in up to 12.5% of cases, most often with meningoencephalitis.[2-4] Pathologic examination of the central nervous system (CNS) revealed inflammatory cell infiltration of the leptomeninges, which induced an immune response.[3-4] However, abnormal gammopathies caused by an immune response have not been reported previously.

We report a case of transient biclonal gammopathy associated with tsutsugamushi meningitis.

Case Report

A 55-year-old man presented with fever and confused mental status for 2 days. His body temperature was 38.6℃ on admission. He had not taken any antibiotics or antipyretics.

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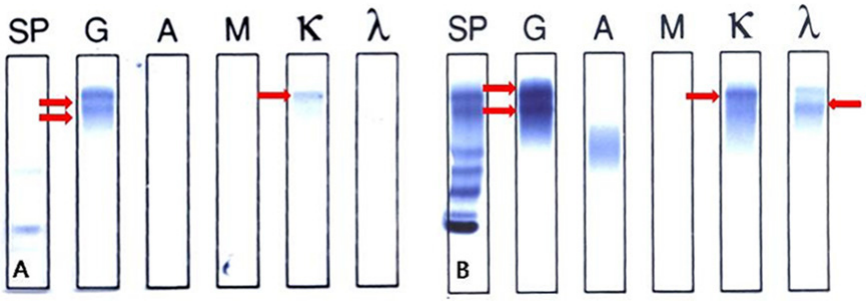

Figure 1. Immunofixation electrophoresis of the patient's CSF (A) and serum (B). Several M components are identified as IgG-κ and IgG-λ bands (solid arrows).

However, he reported a history of chills, myalgia, and skin rash for approximately 5 days prior to his presentation. His medical history was unremarkable, and he had no history of recent respiratory tract infection. He worked as a security manager for an apartment. On physical examination, eschar, lymph node enlargement, or hepatosplenomegaly were not found. Neurological examination showed a drowsy mental status with neck stiffness and papilledema. The functions of cranial nerve and brain stem reflexes were normal. Laboratory results showed a WBC count of $13,8\times10^3/mm^3$, RBC count of $4.2\times10^6/mm^3$, platelet count of $265\times10^3/mm^3$, LDH 68 IU/L, albumin/globulin (A/G) ratio 1.0 (total protein 6.8 g/dL, albumin 3.4 g/dL), AST/ALT 70/87 IU/L, and BUN/Cr 14.4/0.8 mg/dL. No particular manifestation was found in brain MRI and electroencephalography. A serum immunofluorescence assay for antibody to *O. tsutsugamushi* was negative and the titer was <1:20 (normal <1:20). Cerebrospinal fluid (CSF) examination showed WBC count of $80/mm^3$, protein 148 mg/dL, and glucose 67 mg/dL. Although a conservative treatment was done for 5 days, his body temperature remained elevated and a drowsy mental status continued. Repeated laboratory results after 5 days of admission showed WBC count of $11.3\times10^3/mm^3$, RBC count of $3.75\times10^6/mm^3$, platelet count of $284\times10^3/mm^3$, A/G ratio 1.0 (total protein 6.5 g/dL, albumin 3.3 g/dL), AST/ALT 242/102 IU/L, and BUN/Cr 15.1/0.66 mg/dL. CSF examination showed WBC count of $30/mm^3$, protein 94 mg/dL, and glucose 57 mg/dL. Cultures of the CSF for bacteria, acid-fast bacilli, and fungus showed negative results. Cryptococcal antigen test was negative. CSF immunofixation electrophoresis (IFE) showed moderate intensity of distinct IgG-κ band (Figure 1A). Serial serum immunofluorescence assay for antibody to *O. tsutsugamushi* changed from negative to positive (admission day <1:20, 5 days after admission 1:10,240). Serum IFE showed biclonal gammopathy (IgG-κ, IgG-λ) (Figure 1B). Urine IFE was normal. There were no antibodies against hepatitis B and C virus, Epstein-Barr virus, herpes simplex virus, cytomegalovirus (CMV), human immunodeficiency virus (HIV), hantan virus, or *Leptospira*. Bacterial and parasite tests in the blood showed negative results. Tumor markers such as alpha-fetoprotein, carcinoembryonic antigen (CEA), prostate specific antigen (PSA), and cancer antigen (CA) 19-9 were negative.

The patient was treated with an antibiotics (doxycycline) for 14 consecutive days; his symptoms gradually improved, and he was discharged. Although we did not perform a follow up CSF study, serum biclonal gammopathy completely disappeared after 4 months.

Discussion

Scrub typhus is caused by *Orientia* (formerly *Rickettsia*) *tsutsugamushi*, an arthropod-borne obligate intracellular gram-negative organism, which is transmitted through the bite of *Leptothrombidium* mites' (chiggers).[1,2] The key diagnostic feature is the presence of an eschar at the site of chigger bites. However, eschar may not be seen in some cases under actual clinical conditions.[1,3,4]

Although its severity varies considerably, neurological complications of scrub typhus usually result in meningoencephalitis. Pathological examination of the CNS shows an infiltration of mononuclear cells, macrophages or plasma cells to the leptomeninges, which induces an immune response.[2-4] In our case, even after conservative therapy, fever persisted, and leukocytosis and a reversed A/G ratio were observed.

Therefore, we performed an electrophoretic examination, and found abnormal gammopathy associated with the immune response to tsutsugamushi meningitis.

The exact mechanism of immune responses to *O. tsutsugamushi* infection is not clearly defined. However, two possible mechanisms have been proposed: The first mechanism involves a direct invasion of the CNS by *O. tsutsugamushi*, resulting in the production of immunoglobulins. *O. tsutsugamushi* is capable of inducing the production of cytokines such as interleukin (IL)-6 and IL-10. IL-10 is an important differentiation factor for plasma cell formation and immunoglobulin secretion. IL-6 is a major growth factor for myeloma and plasma cells and induces immunoglobulin production.[1,6,7] The second mechanism involves a simple leakage of immunoglobulin from serum into the CSF through damaged blood-CSF barrier.

Transient monoclonal or biclonal gammopathies are associated with immunological disorders or viral infections, such as hepatitis B and C, CMV, HIV, and *Helicobacter pylori*.[5,8-10] In our case, all tests were negative for antibodies of viral disease related to abnormal gammopathy. Furthermore, the patient had no history of immune-mediated disorders, and his responsiveness to antibiotics was good, and abnormal gammopathy completely disappeared. Based on these findings, we suggest that transient biclonal gammopathy is associated with scrub typhus, and it may have a relationship with excessive production of cytokines; however, we need further research to determine how the abnormal gammopathy affects the clinical course in scrub typhus.

In conclusion, this is the first report of transient biclonal gammopathy in serum and CSF of a patient with tsutsugamushi meningitis, and immune response may play a role in the biclonal gammopathy associated with tsutsugamushi meningitis.

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