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【 CASE REPORT 】

Mollaret Meningitis with a High Level of Cytokines in the Cerebrospinal Fluid Successfully Treated by Indomethacin

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Abstract:
A rare case of Mollaret meningitis characterized by four recurrent episodes of aseptic meningitis during a three-year period is reported. The patient showed a high fever and severe headache accompanied by a high level of cerebrospinal fluid (CSF) cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). The symptoms and high CSF cytokines were resolved immediately after introducing indomethacin treatment. Reactivation of the latent virus is considered to be the cause of this rare disease, and indomethacin is believed to inhibit the periodic abnormal generation of eicosanoid in the brain, resulting in a reduction in the fever and subsequent inflammation.

Key words: Mollaret meningitis, recurrent aseptic meningitis, fever, indomethacin, cytokines

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Introduction

Mollaret meningitis was first described by Mollaret in 1944 as a form of aseptic meningitis characterized by recurrent episodes of severe headache, meningismus and a fever. Cerebrospinal fluid (CSF) often shows pleocytosis. The attacks are separated by symptom-free periods that last weeks to months, and the symptoms and signs resolve spontaneously without any neurologic sequelae (1). While viral infections such as herpes simplex virus (HSV) type 2 have been considered as potential causes of this disease (2), the precise etiology and optimal treatment strategy remain unclear.

We herein report a case of Mollaret meningitis in a man who developed his fourth episode of aseptic meningitis during a three-year period with high levels of CSF cytokines successfully treated with indomethacin.

Case Report

A 34-year-old man was admitted to our hospital complaining of a fever, headache, nausea and vomiting. His symptoms began two days before the admission and had been progressively worsening. He had a history of varicella-zoster virus infection and reported that his current symptoms were identical to those of three previous episodes during the past three years, which were diagnosed as aseptic meningitis each time.

The patient was uncomfortable but alert and oriented. A physical examination revealed no pathological findings except for slight neck stiffness and a fever. Non-contrast magnetic resonance imaging (MRI) was negative for acute pathology. Laboratory investigations showed normal blood cell counts and electrolyte levels except for high values of C-reactive protein (1.6 mg/dL), indicating inflammation. A lumbar puncture was performed with an opening pressure of 17 cm H_2O (normal values 7-11 cm H_2O). The CSF was colorless, with 212 cells/mm^3 (91% lymphocyte), 48 mg/dL

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protein and 71 mg/dL glucose (Table). These abnormal data suggest typical meningitis. The patient was diagnosed with aseptic meningitis and admitted to our department for a further examination and treatment.

Because this was his fourth episode of aseptic meningitis in the past three years, the authors suspected the involvement of Mollaret meningitis and conducted a detailed examination. Cranial and spinal MRI and computed tomography (CT) with/without contrast medium were performed for the detection of other potential entities, such as an anatomical defect or tumor. However, these examinations showed no abnormalities. No organisms were seen on CSF Gram staining, and CSF culture also exhibited no growth. The serum IgG, IgA and C3 levels were within the normal range, while the C4 (78 mg/dL) and total complement levels (64 CH50/mL) were slightly above the normal limit. Further blood examinations failed to reveal any auto-immune or infectious diseases; human immunodeficiency virus (HIV), rapid plasma reagin (RPR), antinuclear antibody, anti-DNA antibodies, anti-double stranded (DS) DNA antibody and anti-SSA/SS-B antibody were all negative. We performed a CSF Herpes simplex virus semiquantitative polymerase chain reaction (PCR) examination, but the results were negative. The laboratory findings of CSF with an enzyme-linked immunosorbent assay (ELISA) for pathogenic agent (herpes simplex types 1 and 2, echovirus type 11, coxsackie virus, mumps virus, cytomegalovirus) were negative. The only positive finding with an ELISA was varicella-zoster virus IgG with negative IgM, which denotes a history of infection. A CSF and blood cytokine study revealed that the interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) levels were extremely elevated in the CSF compared to the blood sample (Table).

Table. The Clinical Course of the CSF and Blood Examination.

		Day 1	Day 3	Day 16	Day 30
CSF	Cells (mm^3)	212	477	111	(-)
	(% lymphocytes)	91%	86%	88%	(-)
	Glucose (mg/dL)	71	54	58	(-)
	Protein (mg/dL)	48	157	49	(-)
	IL-6 (pg/mL)	(-)	1,130	2.2	(-)
	TNF-a (pg/mL)	(-)	25.1	<0.5	(-)
Blood	WBC (/uL)	7,700	4,200	6,300	6,100
	CRP	1.6	3.5	0.1	0.0
	IL-6 (pg/mL)	(-)	11.8	2.4	(-)
	TNF-a (pg/mL)	(-)	3.6	1.3	(-)

IL-6: interleukin-6, TNF-a: tumor necrosis factor-alfa, WBC: white blood cell, (-): not examined

Although the patient received empiric treatment with acyclovir and ceftriaxone, he complained of persistent headache and a high fever, even after three days of treatment. A CSF examination performed at day 3 revealed worsening of the findings: 477 cells/mm^3 (86% lymphocyte). We therefore prescribed 75 mg/day of indomethacin according to the literature (3). The fever and symptoms gradually improved after starting indomethacin, and he no longer complained of any headache or fever after Day 7 (Figure). A CSF test performed at Day 15 also showed marked improvement with 111 cells/mm^3, 49 mg/dL protein and 58 mg/dL glucose. The levels of CSF cytokines were also markedly improved (IL-6 2.2 pg/mL, TNF-α <0.5 pg/mL) (Table).

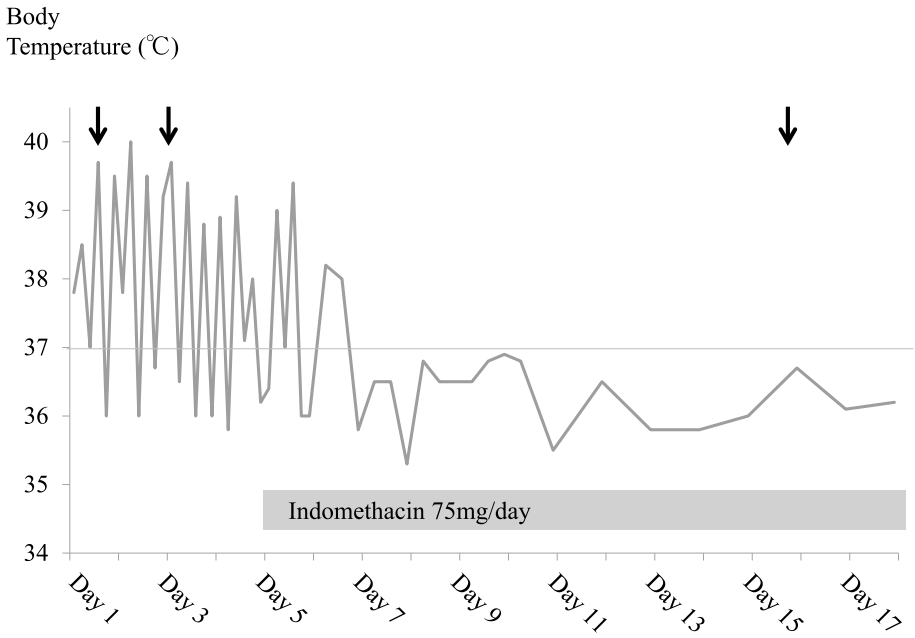

Figure. The temporal profile of the patient's body temperature. After administrating 75 mg/day of oral indomethacin after Day 5, the fever gradually improved to the normal range. The arrow indicates the day of CSF study.

The patient was discharged from our hospital with prophylactic indomethacin administration. He has been followed up at our outpatient clinic. He continued to take indomethacin for one year and became drug-free thereafter without any symptoms of recurrence. In the seven years since then, the patient has not shown similar complaints of these symptoms.

Discussion

In 1962, Bruyn et al. (4) outlined the criteria for a diagnosis of Mollaret meningitis as follows: (1) Recurring episodes presenting with severe headache, meningismus and a fever; (2) pleocytosis in the CSF composed of endothelial cells, neutrophils and lymphocytes; (3) the development of episodes after symptom-free periods of weeks to months; and (4) the absence of a detectable etiological agent. Our patient had aseptic meningitis, a fever and headache, all of which had recurred at intervals of two weeks to two years, with remission of all symptoms within two weeks without any sequelae. Large endothelial cells (Mollaret cells), known to originate from monocytes/macrophages, were not observed in our patient. They are said to be apparent in the first 24 hours, but we detected no such cells because our examination was carried on Day 3. The IgG index, which is calculated as the ratio of CSF/Serum IgG and CSF/Serum albumin, may also be useful for the diagnosis of Mollaret meningitis. Even so, our patient met the criteria and was diagnosed with Mollaret meningitis.

Members of the herpes virus family are thought to be the cause of this rare recurrent episode, and our case also showed a history of varicella-zoster virus infection. Most of the herpes virus family members reported in cases of Mollaret meningitis in the literature were herpes simplex, and this was the first case showing varicella-zoster virus infection. Reactivation of the latent virus nested in the sensory posterior root ganglions is suspected to be responsible. However, the data in this report do not completely prove that varicella-zoster virus was the cause of this symptom. If we performed PCR against varicella-zoster virus, we could have directly proven the activation of the virus in this patient. In addition, an ELISA was only performed once, at the time of admission, and a repeated ELISA might have revealed other virus infections. The antibody index may also be useful for determining the actual infection.

In this report we discovered that IL-6 and TNF-α were markedly elevated in both the CSF and serum during the high-fever period, eventually returning to the normal range after the administration of indomethacin. IL-6 is an interleukin that acts as a pro-inflammatory cytokine. It is secreted by T cells and macrophages and stimulates the immune response, being one of the most important mediators of a fever and the acute phase response. It is capable of crossing the blood brain barrier and initiating the synthesis of prostaglandin (PG)E_2 in the hypothalamus, thereby changing the body's temperature set point. TNF-α is also a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. TNF-α activates the nuclear factor (NF)-κB and mitogen-activated protein kinase (MAPK) pathways in order to advance inflammation and induce cell-damaging signaling. Together with IL-6, TNF-α has a number of effects on various organ systems, such as acting against the hypothalamus by stimulating the release of corticotropin-releasing hormone (CRH), suppressing the appetite and inducing a fever. The immune response against these subclinical viral infections may have activated the excessive production of cytokines and induced the patient's high fever. Recently, Willmann et al. (5) proposed that deficiency of the immune system such as toll-like receptors 3 (TLR-3), may play an important role in the development of Mollaret meningitis. The triggering of TLR-3 is believed to induce an innate immune response by stimulating the production of interferons and activating a variety of cytokines and chemokines. They concluded that a deficiency in TLR3 triggering may cause recurrent meningitis. However, the present report is the first in the English literature to describe the extreme elevation of cytokines, especially in the CSF, during the meningismus period. Not only TLR-3 but also many other factors may be involved in the development of this disease.

To date, many drugs have been administered for the treatment and prophylaxis of Mollaret meningitis, such as acyclovir, colchicine, non-steroidal anti-inflammatory agents, antimicrobials and allopurinol (2). However, none has been proven to have any marked efficacy. Indomethacin is a non-steroidal anti-inflammatory drug commonly used to reduce a fever, pain, stiffness and swelling. It works against the hypothalamus by inhibiting the production of prostaglandin, a molecule known to cause these symptoms. Indomethacin may therefore have inhibited the periodic abnormal generation of eicosanoid in the brain, resulting in a fever reduction. Indomethacin is the only non-steroidal anti-inflammatory agent drug reported to be effective in previous case reports, and there are currently no other non-steroidal anti-inflammatory agents that have been shown to be effective against this disease. We did not prescribe adrenocortical steroid for this patient, which may also be effective in inhibiting the periodic abnormal generation of eicosanoid and reducing cytokine levels. However, we cannot exclude the possibility that the relief of these symptoms was only due to the natural course of this disease, as Mollaret meningitis typically resolves after 3 to 5 days, regardless of treatment.

We believe that improved awareness of the rare disease Mollaret meningitis will allow for the further investigation into the genetic or environmental factors that might predispose patients to its development and facilitate the application of appropriate curative treatment or effective long-term prophylaxis for all afflicted patients.

The authors state that they have no Conflict of Interest (COI).

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