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Case Report Open Access

Mollaret Meningitis with High Level of Cytokines in CSF Successfully Treated by Indomethacin

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Abstract

A rare case of Mollaret meningitis characterized by four recurrent episodes of aseptic meningitis during the 3-year periods were reported. The patient showed high fever and severe headache accompanied by high level of cerebrospinal fluid (CSF) cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alfa (TNF-a). The symptoms and high CSF cytokines were dramatically resolved immediately after inducing indomethacin treatment. Reactivation of the latent virus is considered to be the cause of this rare disease and indomethacin is estimated to inhibit periodic abnormal generation of eicosanoid in the brain resulting in reducing fever and subsequent inflammation.

Keywords: Mollaret meningitis; Recurrent aseptic meningitis; Fever; Indomethacin; Cytokines

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 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]. Although, viral infections such as herpes simplex virus (HSV) type 2 have been considered as one of the cause of this disease [2], the precise etiology and optimal treatment strategy for this rare disease are still unknown. In this report, the authors describe a case of Mollaret meningitis in a man who developed his fourth episode of aseptic meningitis during the 3 year periods with high level of CSF cytokines and was 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 2 days before the admission and had been progressively worsening. He had a past history of zoster herpes, and reported that his current symptoms were identical to 3 previous episodes during the past 3 years which were diagnosed as aseptic meningitis each time. The patient was uncomfortable but alert and oriented. Physical examination revealed no pathological findings except slight neck stiffness and fever. A non-contrast magnetic resonance (MR) imaging was negative for acute pathology. Laboratory investigations showed normal blood cell counts and electrolytes except for the high value of C-reactive protein (1.6 mg/dl), which represents high inflammation in the body. A lumbar puncture was performed with an opening pressure of 17 cm H_2O (normal values 7-11 cm H_2O). The cerebrospinal fluid (CSF) was colorless, with 212 cells/mm^3 (91% lymphocyte), 48 mg/dl protein, and 71 mg/dl glucose. These abnormal data suggest typical meningitis. The patient was diagnosed as aseptic meningitis and admitted to our department for further examination and treatment.

		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)	(-)	1130	2.2	(-)
	TNF-a (pg/ml)	(-)	25.1	<0.5	(-)
Blood	WBC (/ul)	7700	4200	6300	6100
	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	(-)

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

Table 1: The clinical course of the CSF and blood examination.

Because this is his fourth episode of aseptic meningitis in the last 3 years, the authors suspected the involvement of Mollaret meningitis, and have conducted a detailed examination. Cranial and spinal MR imaging and computed tomography (CT) with/without contrast medium was carried out for detection of other possibilities, such as an anatomical defect or tumor. However, the examination showed no abnormality. No organisms were seen on the CSF gram stain and CSF culture also exhibited no growth. Serum IgG, IgA, C3 levels were within the normal range, while C4 (78 mg/dl) and total complement levels (64 CH50/ml) were slightly above the limit line. Further blood examination could not find out any auto-immune and infectious disease; 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. We performed CSF Herpes simplex virus polymerase chain reaction (PCR) examination, but was found to be negative. Laboratory findings of CSF under enzyme-linked immunosorbent assay (ELISA) for pathogenic agent (herpes simple type 1 and 2, echovirus type 11, coxsackie virus, mumps virus, cytomegalovirus) were negative. The only positive finding with ELISA was herpes zoster virus IgG with negative IgM, which denotes past infection of this disease. CSF and blood cytokine study revealed that interleukin (IL)-6 and Tumor necrosis factor-alfa (TNF-a) were extremely elevated in the CSF compared to the blood sample (Table 1).

Although the patient received empiric treatment with acyclovir and ceftriaxone, the patient kept complaining headache and high fever even after 3 days of treatment. The CSF examination undertaken at day 3 revealed worsening of the data; 477 cells/mm^3 (86% lymphocyte). So we decided to prescribe 75 mg/day of indomethacin according to the past literature [3]. The fever and symptom gradually improved after admission of indomethacin, and he no longer complained any headache or fever after Day 7 (Figure 1). His CSF test done at Day 15 also showed marked improvement with 111 cells/mm^3, 49 mg/dl protein and 58 mg/dl glucose. CSF cytokines were also remarkably improved (CSF; IL-6 2.2 pg/ml, TNF-a <0.5 pg/ml). The patient discharged from our hospital with prophylactic indomethacin administration. He has been followed-up at our outpatient clinic. The patient has subscribed indomethacin for one year and became drug free thereafter without any symptom of recurrence. Since then, the patient has not shown similar complaints of the symptom for this 7 years.

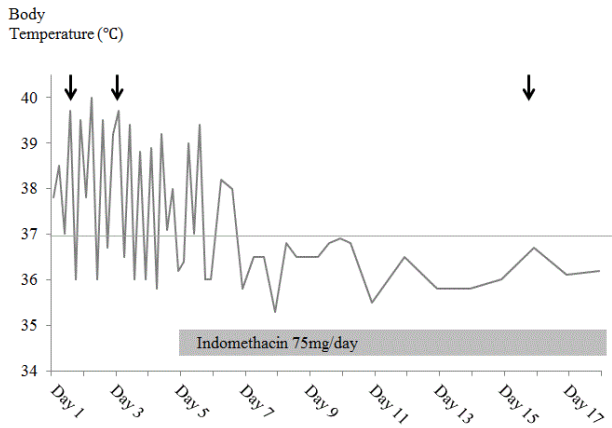

Figure 1: The temporal profile of the patient's body temperature. After administrating 75 mg/day of oral indomethacin after Day 5, the fever gradually improved to the normal range. The arrow indicates the day of CSF study.

Discussion

In 1962, Bruyn et al. [4] outlined the criteria for diagnosis of Mollaret meningitis as follows: (1) Recurring episodes presenting with severe headache, meningismus and fever, (2) Pleocytosis in the CSF composed of endothelial cells, neutrophils and lymphocytes, (3) Development of episodes after symptom-free periods of weeks to months, (4) Absence of a detectable etiological agent. Our patient had aseptic meningitis, fever, and headache, all of which had recurred at interval of 2 weeks to 2 years, with remittance of all symptoms within 2 weeks without any sequelae. Large endothelial cells (Mollaret cells), known to originate from monocytes/marcophages, were not observed in our patient. They are said to be apparent in the first 24 h, we could not find out these cells because our examination was carried out at Day 3. Even so, our patient fulfilled the criteria and was diagnosed as Mollaret meningitis.

Members of the herpes virus family are thought to be the cause of this rare recurrent episode and our case also showed HZV infection. Since most of the herpes virus family reported in the Mollaret meningitis in the literatures are herpes simplex, and this is the first report which showed the HZV infection. Reactivation of the latent virus nested in the sensory posterior root ganglions is suspected to be responsible. In this report we have discovered that IL-6 and TNF-a were markedly elevated in both CSF and serum during the high fever period and was settle down to normal range after administration of the indomethacin. IL-6 is an interleukin that acts as a pro-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response and is one of the most important mediators of fever and of the acute phase response. It is capable of crossing the blood brain barrier and initiating synthesis of PGE2 in the hypothalamus, thereby changing the body's temperature set point. TNF-a is also a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. TNF-a activate NF-kB, MAPK pathways in order to progress inflammation, and also induce cell-damaging signaling. Together with IL-6, TNF-a has a number of actions on various organ systems, for example, they act against hypothalamus by stimulating the release of corticotropin releasing hormone (CRH), suppressing appetite, and inducing fever. We presume that the immune response against these subclinical virus infection may cause the activation of excessive production of cytokines, and induce high fever. Recently, Willmann et al. [5] has proposed that the deficiency of the patient immune system; toll-like receptors 3 (TLR-3), may takes an important role in development of Mollaret meningitis. TLR-3 triggering is believed to induce innate immune response by stimulating the production of interferons and activating a variety of cytokines and chemokines. They concluded that deficiency of TLR-3 triggering may cause recurrent meningitis. However, in this report, we have discovered, first in the English literature, that the cytokines, especially in the CSF, are extremely elevated 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 in the treatment and prophylaxis such as acyclovir, colchicine, non-steroidal anti-inflammatory agents, antimicrobials, allopurinol and so on [2]. However, none of them has been proven to have an influence over the disease. Indomethacin is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. It works against hypothalamus by inhibiting the production of prostaglandin, molecules known to cause these symptoms. So, it is estimated that indomethacin inhibited periodic abnormal generation of eicosanoid in the brain resulting in reducing fever. Indomethacin is the only non-steroidal anti-inflammatory agent drug that was found to be effective in the past case report, and there are currently no other non-steroidal anti-inflammatory agents which is shown to be effective against this disease. However, we cannot exclude the possibility that the relief of these symptoms were only due to the natural course of this disease,

because Mollaret meningitis has typically resolve after 3 to 5 days of treatment.

Conclusion

We regard that improved awareness of this rare disease, Mollaret meningitis, will allow for further investigation into genetic or environmental factors that could predispose patients to the development of Mollaret meningitis and allow appropriate curative treatment or effective long-term prophylaxis for all patients with Mollaret meningitis.

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