Treatment of Histiocytic Necrotizing Lymphadenitis (Kikuchi’s Disease) with Prolonged Fever by a Single Course of Methylprednisolone Pulse Therapy without Maintenance Therapy: Experience with 13 Cases

Katsunobu Yoshioka¹, Tomoko Miyashita¹, Tomoyuki Nakamura¹, Takeshi Inoue² and Keiko Yamagami¹

Abstract

A 26-year-old man was hospitalized with a 1-month history of fever. Cervical lymph node biopsy showed necrosis in the paracortical area with abundant nuclear debris and proliferation of histiocytes. A diagnosis of histiocytic necrotizing lymphadenitis (HNL) (Kikuchi’s disease) was made. He received methylprednisolone pulse therapy (MPT) (0.5 g/day for 3 days) without maintenance therapy and experienced dramatic improvement. We also used MPT for another 12 cases of HNL. All patients became afebrile within 1 day without adverse events. Four patients relapsed after the initial MPT, but only 1 patient relapsed during the following year. Our results suggest that MPT is warranted in HNL patients with prolonged fever.

Key words: histiocytic necrotizing lymphadenitis, Kikuchi’s disease, methylprednisolone pulse therapy, hemophagocytic syndrome

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Introduction

Histiocytic necrotizing lymphadenitis (HNL), or Kikuchi’s disease, is not uncommon, especially in Japan. It predominantly affects the younger population and is characterized by enlarged cervical lymph nodes, high fever, and leukopenia (1). Although the clinical course of HNL is relatively benign and usually self-limiting, some patients experience a daily spiking fever of >40°C for a long period and sometimes progress to hemophagocytic syndrome (HPS). Because prolonged fever can be distressing for patients and force them to take time off from work or school, corticosteroid therapy has been recommended to shorten the febrile duration (2-8). To date, however, no randomized controlled study has been conducted and there is no established regimen of corticosteroid therapy for HNL. Thus, a tapered regimen of oral prednisolone therapy is generally used empirically. However, such a regimen requires several weeks to months to be completed, during which patients must go to a hospital as an outpatient during this period. This can further distress patients who want to return to work or school as quickly as possible.

We used methylprednisolone pulse therapy (MPT) without maintenance corticosteroid therapy in 13 cases of histologically proven HNL with prolonged fever (more than 2 weeks). We provide a review of our cases and discuss the rationale for using MPT.

Case Report

A 26-year-old man was admitted to our hospital with a 1-month history of fever, pain in the neck, and headache. He had been in good health until 1 month previously, when he noted a low-grade fever and general malaise. He visited his family physician and was treated with antibiotic therapy with no noticeable effects. He experienced a daily spiking fever of >39°C, and general malaise worsened. He was then referred to our hospital for further examination and treatment. His physical examination was unremarkable except

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for enlarged and tender posterior cervical lymph nodes. His initial laboratory exam revealed high lactate dehydrogenase (LDH) and C-reactive protein (CRP) levels (302 IU/L and 0.71 mg/dL, respectively). Serum ferritin level was 463.5 ng/mL. Other laboratory results, including white blood cells (WBC) (4,050/µL) and platelets (193,000/µL) were normal. Anti-nuclear antibody (ANA) was negative and serum levels of C3 and C4 were normal, making systemic lupus erythematosus (SLE) unlikely. Sepsis was ruled out by negative cultures for bacteria. Results of serological tests for Epstein-Barr virus (EBV)-related antibodies were as follows: titers of IgG antibody to viral capsid antigen (VCA), 40; EBV-VCA-IgM; 10×; and EB nuclear antigen (EBNA), 20. Because we suspected HNL, we performed a cervical lymph node biopsy, which showed necrosis in the paracortical area with abundant nuclear debris and proliferation of lymphocytes and phagocytic histiocytes (Fig. 1). Malignant lymphoma and tuberculosis were ruled out by histologic findings. Thus, a diagnosis of HNL was made. Because he continued to have a high fever and seemed distressed, he was started on MPT (0.5 g/day for 3 consecutive days) on the fourth day of hospitalization. The patient became afebrile on the next day and his LDH level returned to normal 4 days following the start of MPT. He was discharged 5 days following the start of MPT and did not experience a relapse during the following 3 years, despite the fact that he was not treated with maintenance corticosteroid therapy.

Over the past 8 years, we experienced 12 other similar cases of histologically proven HNL with prolonged fever (more than 14 days), and we have used MPT for these patients. No patient had a history of diabetes mellitus, hypertension, or mental disease. The age, sex, duration of fever, LDH level, WBC count, platelet count, serum ferritin level, ANA titer, and dose and duration of MPT for all cases are shown in Table 1.

The mean age of the patients was 26.7 years, (range, 19

Table 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (days)</th>
<th>sex</th>
<th>febrile period (days)</th>
<th>LDH (IU/L)</th>
<th>WBC count (mL)</th>
<th>platelet count (10^5/µL)</th>
<th>CRP (mg/dL)</th>
<th>Ferritin (ng/mL)</th>
<th>Titer for ANA</th>
<th>dose and duration (days) of MPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>M</td>
<td>30</td>
<td>302</td>
<td>4,050</td>
<td>19.3</td>
<td>0.71</td>
<td>463.5</td>
<td>&lt;40</td>
<td>0.5g×3</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>M</td>
<td>60</td>
<td>420</td>
<td>3,730</td>
<td>26.1</td>
<td>1.9</td>
<td>968.2</td>
<td>&lt;40</td>
<td>0.5g×3</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>M</td>
<td>26</td>
<td>308</td>
<td>4,750</td>
<td>11.3</td>
<td>2.17</td>
<td>625.9</td>
<td>N.D</td>
<td>0.5g×3</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>F</td>
<td>22</td>
<td>444</td>
<td>3,100</td>
<td>14.6</td>
<td>0.3</td>
<td>291</td>
<td>&lt;40</td>
<td>0.5g×3</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>F</td>
<td>16</td>
<td>402</td>
<td>2,386</td>
<td>19.1</td>
<td>0.57</td>
<td>415.5</td>
<td>&lt;80</td>
<td>1.0g×3</td>
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<tr>
<td>6</td>
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<td>M</td>
<td>19</td>
<td>435</td>
<td>4,280</td>
<td>19.1</td>
<td>0.4</td>
<td>760.7</td>
<td>&lt;40</td>
<td>0.5g×3</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>M</td>
<td>26</td>
<td>271</td>
<td>3,200</td>
<td>15.5</td>
<td>1.36</td>
<td>481.7</td>
<td>&lt;40</td>
<td>1.0g×3</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>F</td>
<td>120</td>
<td>200</td>
<td>3,320</td>
<td>13</td>
<td>3.77</td>
<td>642.7</td>
<td>&lt;40</td>
<td>0.5g×3</td>
</tr>
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<td>9</td>
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<td>F</td>
<td>32</td>
<td>434</td>
<td>2,780</td>
<td>33.2</td>
<td>2.6</td>
<td>N.D.</td>
<td>N.D.</td>
<td>0.5g×2</td>
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<tr>
<td>10</td>
<td>19</td>
<td>F</td>
<td>450</td>
<td>540</td>
<td>10.4</td>
<td>0.55</td>
<td>986.3</td>
<td>&lt;40</td>
<td>0.5g×3</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>20</td>
<td>F</td>
<td>189</td>
<td>4,040</td>
<td>27.9</td>
<td>0.24</td>
<td>N.D.</td>
<td>N.D.</td>
<td>0.5g×3</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>F</td>
<td>238</td>
<td>3,020</td>
<td>16.5</td>
<td>1.33</td>
<td>N.D.</td>
<td>N.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>18</td>
<td>F</td>
<td>50</td>
<td>155</td>
<td>4,260</td>
<td>19.4</td>
<td>0.23</td>
<td>N.D.</td>
<td>&lt;40</td>
<td>0.5g×3</td>
</tr>
</tbody>
</table>

LDH: lactate dehydrogenase, WBC: white blood cell, CRP: C-reactive protein, ANA: anti-nuclear antibody, N.D. not detected, MPT: methylprednisolone, M: male, F: female
to 50 years) and the male-to-female ratio was 5:8. Mean duration of febrile period before starting MPT was 34.1 days, (range, 14 to 120 days). The mean LDH, WBC, platelet, and CRP levels were 327 IU/L, 3,300/μL, 189,000/μL, and 1.24 mg/dL, respectively. Serum ferritin level was measured in 9 of 13 patients and 8 patients exhibited high serum ferritin levels. Serologic testing for ANA was done in 9 of 13 patients and results were negative in all but 1 patient (in case 5, the titer was mildly positive, i.e., 80). Serologic tests for EBV-VCA-IgM were negative in all patients. We measured EBV-DNA copies in peripheral blood mononuclear cells using real-time polymerase chain reaction in case 5 because the titer for EBV-VCA-IgG was very high (640) and she had a history of HPS at the age of 9. The value was as high as 3.3×10^5 copies/mL. We measured EBV in 2 other patients (cases 1 and 8), but the results were negative. A dramatic response was obtained after MPT, and all patients became afebrile within 1 day with no apparent adverse events. Only 1 patient relapsed during the following year (case 12). However, another 3 patients relapsed after 2 years (case 13), 5 years (case 6), and 6 years (case 4) after the initial MPT. We repeated MPT in 2 of these patients which lead to a favorable response. Another 2 patients recovered without the use of corticosteroids.

Discussion

The differential diagnosis of HNL includes malignant lymphoma, tuberculosis, and SLE, all of which can be associated with enlarged lymph nodes, fever, and leukopenia. However, histologic findings in the present cases were sufficient to rule out malignant lymphoma and tuberculosis. SLE can be associated with lymphadenitis which mimics HNL. As the prognosis and treatment of HNL and SLE are different, it is important to differentiate these two entities. To help with this differentiation, serologic tests for ANA were done in 9 of 13 patients. The negative ANA test results together with the clinical presentation of the patients did not meet the criteria for a diagnosis of SLE.

Although the etiology of HNL is not completely known, viral infections are the most suggested causative agent. Among them, some reports indicate EBV as a causative agent (9, 10), although other reports do not support these findings (11, 12). Although EBV-DNA in the peripheral blood was high in case 5, it is not conclusive whether EBV was a causative agent of HNL or just occurred coincidentally. In either case, careful follow-up is mandatory in such patients.

The characteristic histopathologic findings of HNL include necrosis in the paracortical area with abundant nuclear debris with proliferation of phagocytic histiocytes. Findings of nuclear debris suggest that cell death in HNL is attributed to apoptosis. Serum concentrations of some inflammatory cytokines such as interleukin 6, Fas ligand (13), and interferon γ (14) in patients with HNL have been reported to be increased during the active phase of HNL. These findings suggest that the essence of HNL is the activation of histiocytes, which is triggered by a viral infection and produces excessive inflammatory cytokines. Excessive inflammatory cytokines not only cause the various symptoms of HNL but also further activate histiocytes. Thus, a vicious cycle is formed, and the febrile period is prolonged.

There are several reports of HPS associated with HNL (2, 7, 8, 15, 16). HPS was originally described as a response to viral infections (17). Following the original report, HPS has been reported with bacterial, fungal, and viral infections. The most consistent histopathologic feature in HPS is a proliferation of mature histiocytes that exhibit prominent phagocytosis. It has been reported that in HPS, the prominent phagocytic histiocytes are reactive and are stimulated by T cells (18). Furthermore, many of the findings in HPS may also be due directly or indirectly to cytokines produced by proliferating T-cells and reactive phagocytic histiocytes. Thus, the clinicopathological features of HPS are similar to those of HNL and it is not surprising that some patients with HNL progress to HPS. Some researchers even consider that HPS is a symptom of and not a complication of HNL (7). In case 10, there was severe leukopenia (540/μL) together with mild thrombocytopenia (10,400/μL) and high serum ferritin level (968.3 ng/mL). The production of ferritin is induced by inflammatory cytokines that are released by activated macrophages and a high serum ferritin level is one of the characteristics of HPS. Although bone marrow aspiration was not performed, there is a high possibility of the coexistence of HPS in this patient. Furthermore, serum ferritin levels were high in 8 of 9 patients. Therefore, therapeutic strategies for HNL should be focused on avoiding the progression to potentially fatal HPS as well as relieving clinical symptoms.

One of the mechanisms of actions of corticosteroids is to decrease the production of histiocyte-derived cytokines. Therefore, it is reasonable to consider that corticosteroids are the drug of the choice for the treatment of HNL. However, controversy still surrounds the duration of treatment and appropriate dosage. Anti-inflammatory and immunosuppressive actions of corticosteroids are initiated by binding of corticosteroids to cytoplasmic receptors. To interrupt the vicious cycle described above, it is important to occupy the corticosteroid receptor completely for a certain period. The precise mechanism of beneficial actions of MPT is unclear. However, considering that MPT is sometimes effective despite a failure to respond to ordinary oral corticosteroid therapy in various diseases, corticosteroid receptors appear to be completely occupied by MPT for a longer period than seen with ordinary oral prednisolone therapy.

Currently, there is no standardized therapeutic regimen for HNL and a tapered regimen of oral prednisolone therapy (initial dose: 0.5-2 mg/kg) is generally used empirically (2-8). However, such a regimen takes several weeks to months to complete, the response to prednisolone is not necessarily fast, and not all patients respond to oral prednisolone therapy (6, 7). To our knowledge, there is only one...
previous case report, in which MPT was used for HNL (7). In that report, a 37-year-old woman with a 2-year history of SLE developed HPS associated with HNL. She did not respond to oral prednisolone therapy but MPT had an excellent effect. Because most of the patients with HNL are young, patients are forced to take a time off from work or school for fairly long period. Because our trial is not a randomized, controlled study, it is inconclusive whether MPT is superior to a tapered regimen of corticosteroids in terms of prognosis. However, considering that all patients treated by MPT showed an immediate effect, maintenance corticosteroid therapy was unnecessary, and no adverse events were observed, MPT may be a better option, as it does not require a long treatment period. It is conceivable that early relapse (within 1 year) may be related to the treatment option, whereas late relapse is not. In the present study, only 1 patient relapsed during the following year, suggesting that MPT is not associated with a high relapse rate. As a result, MPT may be a better option, as it does not require a long treatment period. It is conceivable that early relapse (within 1 year) may be related to the treatment option, whereas late relapse is not. In the present study, only 1 patient relapsed during the following year, suggesting that MPT is not associated with a high relapse rate. As a result, MPT should be considered the first-line of treatment if the patient appears distressed and leukopenia progresses. Because of its simplicity and lack of adverse events, MPT can be repeated even if a relapse occurs.

At the beginning of our trial, 1 g/day of methylprednisolone was given for 3 consecutive days. The excellent response prompted us to reduce the dose of methylprednisolone to 0.5 g/day, and efficiency was unchanged. Furthermore, in case 9, 0.5 g/day of methylprednisolone was given for 2 consecutive days with an excellent response. Thus, the optimal dose and duration of the MPT is not known, and further studies are needed to clarify this issue.

In summary, we have reported 13 cases of histologically proven HNL with prolonged fever that dramatically responded to MPT. Our results suggest that a trial of MPT is warranted in HNL patients with prolonged fever lasting for more than 2 weeks despite treatment with nonsteroidal anti-inflammatory drugs after the possibility of malignant lymphoma and tuberculosis have been ruled out.

References