Cytomegalovirus Colitis Following Immunosuppressive Therapy for Lupus Peritonitis and Lupus Nephritis

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Abstract

We report a woman with lupus nephritis complicated with lupus peritonitis and cytomegalovirus (CMV) colitis. Diagnosis of lupus peritonitis was made by abdominal computed tomography scan, colonoscopy, and ascitic fluid analysis. Steroid and cyclophosphamide therapy resulted in the improvement of severe lupus nephritis and peritonitis. Thereafter, she developed multiple colonic ulcers as diagnosed by colonoscopy and positive CMV antigenemia assay. Treatment with ganciclovir resulted in the disappearance of colonic lesions. The low cluster of differentiation (CD)4+ lymphocyte count (41/mm3) suggested that the cell-mediated immunity of this patient was comparable to that seen in patients with acquired immunodeficiency syndrome (AIDS).

Key words: systemic lupus erythematosus, CMV antigenemia, colonoscopy, CD4, ganciclovir, compromised host

Introduction

Lupus peritonitis is a comparatively rare but important gastrointestinal complication of systemic lupus erythematosus (SLE); it can be diagnosed by analysis of ascitic fluid (1). Treatment of lupus peritonitis usually requires strong immunosuppressive therapy (2). Cytomegalovirus (CMV) infection is a frequent and sometimes life-threatening complication in immune compromised patients such as those with acquired immunodeficiency syndrome (AIDS) (3). Patients with lupus peritonitis are prone to develop CMV disease after aggressive treatment with immunosuppressive agents. Here, we report a patient with CMV colitis, which developed after immunosuppressive therapy for severe lupus nephritis and lupus peritonitis. CMV colitis was diagnosed by colonoscopy and CMV antigenemia assay, and was successfully treated by ganciclovir.

Case Report

A 30-year-old woman was admitted to our hospital for the fifth time because of diarrhea, abdominal pain, nausea, vomiting, and hypocomplementemia on October 28, 1999. She was first hospitalized in September 1996 for fever, lymphadenopathy, and hepatosplenomegaly. Although a definitive diagnosis was not made, the symptoms subsided after treatment with prednisolone (PSL). On her second admission in November 1996, insulin-dependent diabetes mellitus was diagnosed; she has been treated with insulin since that time. On her third admission in November 1997, she was suffering from central nervous system disturbances, nephrotic syndrome, and joint pain; test results for antinuclear antibody (ANA) and antiphospholipid antibody were positive, and SLE was diagnosed. A renal biopsy was performed and the diagnosis of lupus nephritis (World Health Organization class Vb) was established. The patient was treated with steroid pulse therapy followed by oral PSL and mizoribine. This resulted in the disappearance of peripheral edema and improvement of laboratory test results. She was discharged in May 1998 on maintenance PSL (20 mg/day). However, tapering of PSL to 15 mg/day was associated with increased proteinuria and worsening of hypocomplementemia. She was admitted for the fourth time in January 1999. Steroid pulse therapy followed by oral PSL treatment resulted in improvement of serum complement levels. However, her proteinuria was unchanged. She was discharged from the hospital in March 1999 on a PSL dose of 25 mg/day. Although PSL was tapered slowly, when PSL was reduced to 10 mg/day, gastro-
Table 1. Laboratory Findings on Admission

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Immunological examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 4,950/mm³</td>
<td>CRP 1.5 mg/dl</td>
</tr>
<tr>
<td>RBC 486×10⁶/mm³</td>
<td>Immune Complex 6.9 µg/ml</td>
</tr>
<tr>
<td>Plt 41.9×10⁴/mm³</td>
<td>Anti-nuclear antibody 40x</td>
</tr>
<tr>
<td>Hb 14.2 g/dl</td>
<td>Anti-DNA antibody &lt;2 IU/ml</td>
</tr>
<tr>
<td>Ht 39.9%</td>
<td>Anti-Sm antibody (-)</td>
</tr>
<tr>
<td></td>
<td>CH₅₀ 13 U/ml</td>
</tr>
<tr>
<td>Blood Chemistry</td>
<td>C₃ 23 mg/dl</td>
</tr>
<tr>
<td>T.P. 5.2 g/dl</td>
<td>C₄ 3 mg/dl</td>
</tr>
<tr>
<td>Albumin 2.6 g/dl</td>
<td>Immunoglobulin G 993 mg/dl</td>
</tr>
<tr>
<td>T. Bil. 0.3 mg/dl</td>
<td>Immunoglobulin A 295 mg/dl</td>
</tr>
<tr>
<td>AST 16 U/l</td>
<td>Immunoglobulin M 41 mg/dl</td>
</tr>
<tr>
<td>ALT 7 U/l</td>
<td>Urinalysis</td>
</tr>
<tr>
<td>LDH 451 U/l</td>
<td>Protein (3+)</td>
</tr>
<tr>
<td>BUN 20 mg/dl</td>
<td>Sugar (1+)</td>
</tr>
<tr>
<td>Cr 1.1 mg/dl</td>
<td>Occult blood (1+)</td>
</tr>
<tr>
<td>Na 136 mEq/l</td>
<td>Protein/day 4.52 g/day</td>
</tr>
<tr>
<td>K 3.3 mEq/l</td>
<td>Creatinine clearance 63.8 l/day</td>
</tr>
<tr>
<td>Cl 100 mEq/l</td>
<td>N-acetylgalactosaminidase 9.5 U/l</td>
</tr>
<tr>
<td>T. Chol. 200 mg/dl</td>
<td>β₂ microglobulin 1,210 µg/l</td>
</tr>
<tr>
<td>T.G. 354 mg/dl</td>
<td>Blood sugar 101 mg/dl</td>
</tr>
<tr>
<td>Blood sugar 101 mg/dl</td>
<td>HbA,C 9.0%</td>
</tr>
</tbody>
</table>

T.P.: total protein, T. Bil: total bilirubin, AST: aspartate
aminotransferase, ALT: alanine aminotransferase, LDH: lactate
dehydrogenase, BUN: blood urea nitrogen, Cr: serum
creatinine, T. Chol.: total cholesterol, T.G.: triglyceride,
HbA,C: glycylated hemoglobin, CRP: C-reactive protein,
CH₅₀: complement activity.

intestinal symptoms such as diarrhea, abdominal pain, nausea
and vomiting, and hypocomplementemia progressed. She
was admitted to our hospital for the fifth time in October
1999.

On admission, blood pressure was 118/68 mmHg, pulse
rate was 120 beats/min with a regular rhythm, and tempera-
ture was 37.1°C. Physiological examination showed pretibial
pitting edema. The lower abdomen was distended due to
ascites. The abdomen was tender, but there was no rebound
tenderness or muscle guarding. Anemia, jaundice, cyanosis,
and skin lesions were not detected. Results of a neurolog-
cal examination were negative.

Results of laboratory tests indicated nephrotic syndrome
and hypocomplementemia (Table 1) with total protein of 5.2
g/dl, albumin 2.6 g/dl, blood urea nitrogen 20 mg/dl, serum
creatinine 1.1 mg/dl, and urinary protein excretion of 4.52
g/day. ANA was 40x (homologous), but anti-DNA antibody
was negative. A marked decrease in complement levels was
noted (complement activity [CH₅₀], 13 U/ml; C₃, 23 mg/dl;
C₄, 3 mg/dl). Serum immune complex (IC) levels were elev-
ated (6.9 µg/ml). The blood cell count was normal with
white blood cell count, 4,950/mm³; red blood cell count,
486×10⁶/mm³, lymphocyte count, 822 /mm³; hematocrit,
39.9%; and platelet count, 41.9×10⁴/mm³. Results of plain
chest X-ray film and electrocardiogram were normal.

A computed tomography scan of the abdomen showed
marked wall thickness of the small intestine and the entire
colon (Fig. 1), and colonoscopy revealed edematous wall
thickening at the same lesion. Analysis of ascitic fluid showed
the exudative ascitic fluid, that is to say, total protein,
2.1 g/dl (ascitic fluid/serum protein ratio, 0.53) and lac-
tate dehydrogenase (LDH), 443 U/l (ascitic fluid/serum LDH
ratio, 0.92). Low complement levels (CH₅₀, 0 U/ml; C₃,
6 mg/dl; C₄, 2 mg/dl) and slightly elevated IC levels (3.4
µg/ml) were also seen in the ascitic fluid. Although ANA
was not examined, anti-DNA antibody was slightly elevat-
ed for the ascitic fluid (5 IU/ml). Cytologic examination of
the fluid showed the presence of erythrocytes (1+) and mononu-
uclear leukocytes (2+) but no malignant cells; results of a bac-
terial culture were negative. Based on the above findings, a
diagnosis of lupus peritonitis was made (1). Accordingly, the
patient received steroid pulse therapy (M-PSL 500 mg/day,
drip intravenous) for 3 consecutive days followed by oral ad-
ministration of PSL 40 mg/day. However, the gastrointesti-
nal symptoms did not improve. Consequently, the dose of
oral PSL was increased to 60 mg/day. Three weeks of such
therapy resulted in improvement of the gastrointestinal
symptoms and a marked fall in proteinuria to 0.3 g/day. The
same dose of oral PSL was continued for 6 weeks, and then
tapered gradually to 40 mg/day over 2 weeks, based on nor-
malization of serum complement levels (CH₅₀, 49 U/ml; C₃,
47 mg/dl; C₄, 20 mg/dl) (Fig. 2). Continuation of PSL at 40
mg/day for 1 week, however, showed a decreasing tendency
of complement levels (CH₅₀, 33 U/ml; C₃, 33 mg/dl; C₄, 12
mg/dl). Therefore, intravenous (IV) cyclophosphamide
(CPA) pulse therapy (500 mg/day, drip intravenous) was ad-
ministered (Fig. 2) (4). This treatment resulted in the com-
plete disappearance of subjective gastrointestinal symptoms
and ascites, and prevented further falls in serum complement
levels. CT scan of the abdomen showed no colonic wall
thickness.
Figure 2. Clinical course after the present admission. PSL: prednisolone, M-PSL: methylprednisolone, CPA: cyclophosphamide, GCV: ganciclovir, CMV Ag: cytomegalovirus antigenemia.

A follow-up colonoscopy, performed on January 17, 2000, showed multiple colon ulcers (Fig. 3). Although a biopsy specimen taken during the colonoscopy did not show the inclusion body of CMV, the CMV antigenemia assay was positive (10 positive leukocytes/1.5×10⁵ total leukocytes) (Fig. 2). Under the diagnosis of CMV colitis, IV ganciclovir was administered at 400 mg/day for 15 consecutive days. This treatment resulted in the disappearance of multiple colonic ulcers and negative results on a CMV antigenemia assay. Subsequently, results of the CMV antigenemia assay were positive 3 times after the discontinuation of IV ganciclovir therapy, and became negative again following resumption of ganciclovir therapy (Fig. 2). The lymphocyte count and the cluster of differentiation (CD)4+ lymphocyte count were 148/mm³ and 41/mm³, respectively, on May 22, 2000. The CMV antigenemia level was kept low by oral administration of ganciclovir (250 mg/day). At that time, the lymphocyte count and CD4+ lymphocyte count were slightly elevated to 325/mm³ and 83/mm³, respectively. Serum complement levels, lupus peritonitis, and lupus nephritis were controlled and she was discharged.

Figure 3. Colonoscopy on January 17, 2000. Note the presence of edema, congestion and multiple ulcers in the sigmoid colon.
from the hospital on July 13, 2000.

Discussion

The incidence of gastrointestinal involvement in patients with SLE varies from 10% to 40% (5). Ascites occurs rarely in SLE patients (8% to 11%), often as a manifestation of nephrotic syndrome (5). In SLE, ascites can be due to many other complications such as lupus peritonitis, pancreatitis, mesenteric vasculitis, pericarditis, protein-losing enteropathy, and malignancy (5). Analysis of ascitic fluid, together with evaluation of gastrointestinal symptoms, is useful for the differential diagnosis of underlying diseases. The complement level of the ascitic fluid is low with nephrotic syndrome, liver cirrhosis, and peritonitis carcinomatosa (6, 7). However, the complement level of the ascitic fluid in this case was remarkably low, and consumption by this lesion was remarkable. These findings lead to the diagnosis of lupus peritonitis.

Nephrotic syndrome is associated with transudative ascitic fluid and the patient usually does not present with abdominal pain. On the other hand, lupus peritonitis is accompanied by abdominal pain and analysis of ascitic fluid often shows exudative fluid with high levels of anti-DNA antibody and low complement levels. Moreover, ascites due to lupus peritonitis is steroid-responsive (1, 5). The differentiation between lupus vasculitis and lupus peritonitis is difficult. In lupus vasculitis, ischemic necrosis results in ulceration and hemorrhage of mucosa and submucosa, where lymphocytes, plasma cells and neutrophils infiltrate. The depositions of IC by immunohistochemistry lead to the definitive diagnosis of lupus vasculitis. On colonoscopy, both multiple round discrete ulcers, so called punched-out ulcers, and larger, deeper and variable-shaped ulcerations have been described (8).

In the present case, the patient had nephrotic syndrome but presented with severe abdominal pain. Examination of ascitic fluid samples showed exudative fluid containing low levels of complement. Administration of high doses of PSL markedly improved abdominal symptoms and ascites. Colonoscopy revealed edematous wall thickening, but did not reveal any ulcers. Thus we considered that the ascites was caused by lupus peritonitis. The inadequate response to initial PSL treatment was probably related to poor absorption of oral PSL due to marked edema of the gastrointestinal tract.

Following the successful control of lupus activity by high-dose PSL, we faced 2 conflicting problems. On one hand, high-dose PSL therapy might cause unfavorable adverse effects such as gastrointestinal tract bleeding and opportunistic infections. On the other hand, SLE seemed to be uncontrollable by maintenance doses of PSL, as episodes recurred repeatedly at 10 to 15 mg/day of PSL. To solve these problems, CPA pulse therapy was used. In this regard, Boumpas et al (4) reported that pulse CPA is more effective than pulse M-PSL in the preservation of renal function and prevention of exacerbation of severe lupus nephritis. Furthermore, Bitran et al (9) reported that the addition of CPA to steroids improves the outcome of lupus peritonitis with ascites. In the present case, the CPA pulse therapy of two times allowed tapering of the PSL therapy without exacerbating the lupus nephritis or lupus peritonitis.

Aggressive immunosuppression resulted in marked clinical improvement, but was associated with the development of CMV colitis. Previous studies have reported that the incidence of CMV infection in Japanese children younger than 2 years is more than 90% and that a large proportion of these cases subsequently become asymptomatic carriers of CMV (10). However, overt CMV infection can develop in patients with disordered cell-mediated immunity such as those with organ transplants, AIDS, or on immunosuppressive therapy. Thus, early diagnosis and treatment of overt CMV infection is important because the condition is life-threatening in compromised hosts.

Recent studies have emphasized the usefulness of the CMV antigenemia assay in the diagnosis, monitoring, and treatment of immune compromised patients (10, 11). The CMV antigenemia assay is designed to detect leukocyte intranuclear CMV antigen using monoclonal antibody against CMV immediate early antigen (IEA). Active proliferation of CMV results in the increased production of IEA. Therefore, positive leukocyte counts reflect the activity of overt CMV infection. CMV antigenemia assay is highly sensitive and becomes positive rapidly during the early stages of the disease; more than one positive leukocyte/1.5x10^5 total leukocytes is clinically significant (11).

Although CMV colitis is a common viral infection that typically occurs during the course of human immunodeficiency virus (HIV) infection, manifesting as intermittent diarrhea accompanied with fever and weight loss (12), CMV colitis complicated with SLE is relatively rare (13, 14). Here, the differential diagnosis of lupus vasculitis and CMV colitis becomes a problem in the present case. Intermittent diarrhea accompanied with fever and weight loss is the common clinical symptom between lupus vasculitis and CMV colitis (8, 12). Dieterich and Rahmin reported that 41% of the patients present with a localized and patchy colitis, and 34% of the patients had a diffuse colitis as well as the present case (15). Moreover, the colonoscopic findings of CMV colitis usually appears as a mucosal erosion or ulceration (16). Therefore, the differentiation of lupus vasculitis and CMV colitis is difficult. Although the final decision for CMV colitis is due to a characteristic cytopathic effect [a large 25- to 35 μm cell containing a basophilic intranuclear inclusion, the so-called owl’s eye effect (16)], it was not detected in the present case. In the present case, the diagnosis of CMV colitis was made by colonoscopy, which showed multiple colonic ulcers and positive CMV antigenemia; further, the activity of SLE was controlled. IV administration of ganciclovir resulted in almost complete disappearance of multiple colonic ulcers and negative CMV antigenemia assay. Ganciclovir, an acyclovir derivative, is effective in approximately 75% of cases (17). The initial treatment of active CMV infection with
ganciclovir requires daily IV administration via a central line for several weeks. Recently, Spector et al (3) reported that oral ganciclovir significantly reduces the risk of CMV disease including CMV colitis in advanced AIDS patients. Therefore, we used oral administration of ganciclovir in the present case.

Development of overt CMV infection depends on the CD4+ lymphocyte count in immune compromised patients. Although there is no conclusive report on the relationship between CMV infection and a decrease in the CD4+ lymphocyte count in SLE, several studies have reported a correlation between these cells and AIDS. Spector et al (3) proposed the definition of immunocompromised AIDS patients with a history of an AIDS-defining opportunistic infection as: “patients with CMV infection and CD4+ lymphocyte count <50 or 100/mm³”. Dieterich and Rahmin (15) reported that CMV colitis occurs when the CD4+ lymphocyte count falls below 100/mm³ in HIV infection. In the present case, the CD4+ lymphocyte count was 41/mm³, suggesting a greatly disordered cell-mediated immunity as seen in severe AIDS patients. The remarkable decrease in CD4+ lymphocytes may be the reason that aggressive treatment with immunosuppressive agents was frequently needed for the control of SLE and for the frequent relapse when PSL was tapered. In this regard, Yoshihara et al (10) reported that CMV antigenemia became positive in 9 of 15 patients with collagen vascular diseases following treatment with PSL at a dose exceeding 30 mg/day, suggesting that overt CMV infection frequently occurs during immunosuppressive therapy.

In summary, we reported a case of lupus nephritis with severe lupus peritonitis that was barely controlled by high-dose corticosteroid therapy and CPA. She developed CMV colitis after strong immunosuppressive therapy was initiated. Colonoscopy and analysis of ascitic fluid were useful for the diagnosis of lupus peritonitis. Early detection of CMV colitis was possible by CMV antigenemia assay and colonoscopy. IV and oral ganciclovir were effective in the treatment of CMV colitis. Determination of the CD4+ lymphocyte count was useful for determining the level of cell-mediated immunity.

References