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CASE REPORT

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Extremely high levels of C-reactive protein in patients with acute lupus serositis

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Abstract We present the cases of two patients (19- and 40-year-old women) with systemic lupus erythematosus (SLE) who showed marked elevation of C-reactive protein (CRP). In both patients, pleural and/or peritoneal effusions were caused by lupus serositis. Methylprednisolone pulse therapy was effective in improving the serositis and normalizing CRP. Although it is generally considered that the CRP response is relatively weak in lupus patients, these cases suggest that a strong CRP response can occur in a subset of SLE.

Key words C-reactive protein (CRP) · Serositis · Systemic lupus erythematosus (SLE)

Introduction

In patients with systemic lupus erythematosus (SLE), serositis is a common complication that often recurs.[1–3] Although peritoneal involvement has been described in only a few case reports, evidence of peritoneal inflammation has been found at autopsy in up to 60% of patients with SLE.[1] Immune-complex-mediated tissue injury and vasculitis have been proposed as possible mechanisms for the pathogenesis of peritoneal inflammation. Lupus peritonitis manifests as ascites and/or abdominal pain. Such abdominal symptoms are sometimes misleading, since they lack specific signs.

Many SLE patients do not show a significant elevation in C-reactive protein (CRP) levels even though other clinical and laboratory findings are highly suggestive of active disease. However, there have been previous reports that lupus patients who have serositis or chronic arthritis tend to show moderately elevated levels of CRP.[4,5] In this report, we describe two SLE patients whose sera displayed extremely high levels of CRP. Both patients had pleural and abdominal effusion due to serositis caused by SLE. Laboratory data and clinical symptoms responded very well to methylprednisolone pulse therapy.

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Case 1

A 19-year-old Japanese woman was admitted to our hospital in December 1999 with fever and diarrhea. Prior to this episode, a diagnosis of SLE had been made in February 1999 after the following findings: butterfly rash, antinuclear antibody ×2560 (speckled); anti-dsDNA antibody 140 EU/l (normal, less than 10 EU/l), thrombocytopenia of $7.8 \times 10^4/mm^3$; lupus nephritis of WHO-II on renal biopsy. Prednisolone (0.5 mg/kg per day) was administered for 4 weeks and then tapered gradually to 10 mg/day. The patient had been treated with a maintenance dose of prednisolone (10 mg/day) until the second admission in December 1999.

On admission, a physical examination showed fever (temperature 38.0°C) and large amount of ascites. A chest X-ray revealed bilateral pleural effusion (Fig. 1a). Laboratory data were as follows: hemoglobin (Hb) 11.2 g/dl; hematocrit (Hct) 33.5%; WBC $17300/mm^3$ (neutrophils 91%, monocytes 2%, lymphocytes 7%, atypical lymphocytes 0%); Plt $29.6 \times 10^4/mm^3$; total protein 6.1 g/dl; albumin 3.1 g/dl; GOT 31 IU/l; GPT 12 IU/l; lactic dehydrogenase (LDH) 732 IU/l; alkaline leukocyte phosphatase (ALP) 559 IU/l; total bilirubin 0.9 mg/dl; total cholesterol 143 mg/dl; blood urea nitrogen (BUN) 9 mg/dl; creatinine 1.5 mg/dl; Na 134 mEq/l; K 4.2 mEq/l; Cl 94 mEq/l; CRP 26.4 mg/dl. Antinuclear antibodies were positive at ×2560 (speckled), anti-dsDNA antibodies were 10 EU/l, and CH_{50} was 8.9 IU/l (normal, 30–45 IU/l). Anti-Sm, ribonucleoprotein (RNP), anticardiolipin antibodies, and p- and c-antineutrophil cytoplasmic antibodies (ANCA) were negative. Urinalysis showed proteinuria of 0.9 g/day with no casts. Cultures from

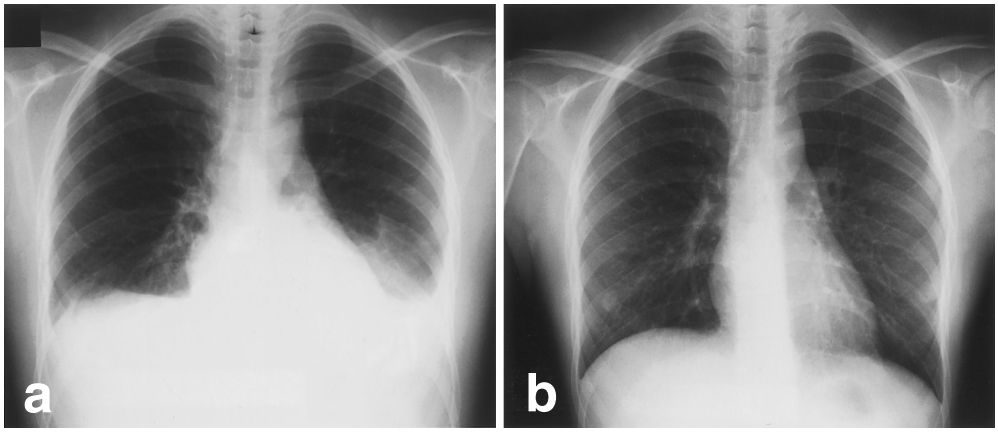

Fig. 1a,b. Chest X-ray films of case 1 **a** before and **b** after steroid pulse therapy show the disappearance of pleural effusion after therapy

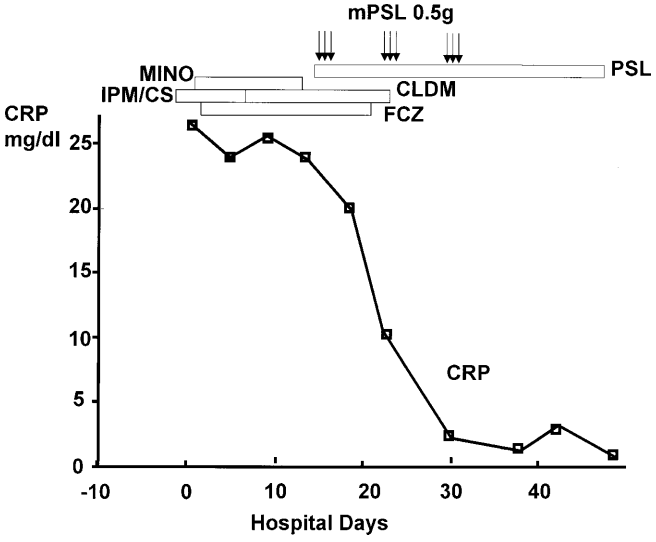

Fig. 2. Clinical course of case 1. *mPSL*, methylprednisolone; *PSL*, prednisolone; *MINO*, minocycline; *IPM/CS*, imipenem/cilastatin; *FCZ*, fluconazole; *CRP*, C-reactive protein; *CLDM*, clindamycin

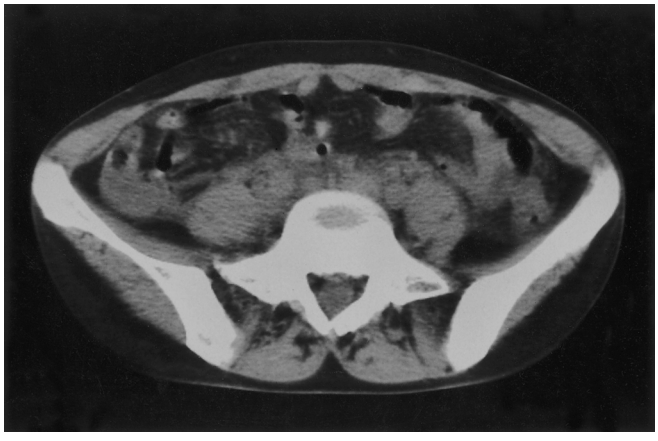

Fig. 3. Ascites and intestinal edema in case 2 as shown on abdominal CT

blood, urine, and sputum were all negative for infectious organisms. Abdominal paracentesis revealed a clear, yellow fluid with a total protein of 3.7 g/dl. Ascitic fluid cytology was class 1. Culture for bacteria was negative. Thoracocentesis also showed a clear, yellow fluid with a total protein of 2.7 g/dl, and with no evidence of infectious organisms. Moreover, several antibiotics and antifungal drugs were ineffective for improving her clinical symptoms and CRP. A diagnosis of lupus pleuritis and peritonitis was made. During the observation period, pleural effusion and ascites increased and the patient became dyspneic. Methylprednisolone pulse therapy was initiated. The therapeutic regimen was as follows: 500 mg/day of methylprednisolone for 3 consecutive days, followed by 0.5 mg/kg/day of oral prednisolone for 4 days. This 1-week regimen was repeated three times. This ameliorated the patient's clinical symptoms, including fever, and pleural and peritoneal effusion (Fig. 1b). Her CH_{50} and CRP gradually returned to normal levels (Fig. 2).

Case 2

A 40-year-old Japanese woman was admitted to our hospital in May 1996 because of fever (temperature 39.0°C) and severe abdominal pain. She had suffered from Raynaud's phenomenon, arthritis, and photohypersensitivity since February 1996. On admission, physical examination showed vascular bruit in her epigastric region. Chest computed tomography (CT) showed pleural and pericardial effusion. Abdominal CT showed intestinal edema and acsites (Fig. 3). Laboratory data were as follows: Hb 10.7 g/dl; WBC 6500/mm^3 (neutrophils 80%, monocytes 14.5%, lymphocytes 5.5%, atypical lymphocytes 0%); Plt 19.4 × 10^4/mm^3; total protein 6.5 g/dl; albumin 3.5 g/dl; GOT 24 IU/l; GPT 13 IU/l; LDH 721 IU/l; ALP 170 IU/l; creatine phosphokinase (CPK) 47 IU/l; total cholesterol 148 mg/dl; BUN 11 mg/dl; creatinine 0.6 mg/dl; Na 135 mEq/l; K 4.0 mEq/l; Cl 99 mEq/l; CRP 31.3 mg/dl. Antinuclear antibodies were positive at ×1280 (speckled), anti-ds DNA antibodies were 10 EU/l, anti-RNP antibodies were 303 EU/l (normal, less than 20 EU/l), and CH_{50} was 54.6 IU/l. Anti-Sm antibodies, anticardiolipin antibodies, and p- and c-ANCA were negative. Urinalysis showed proteinuria of 0.9 g/day. Bloody

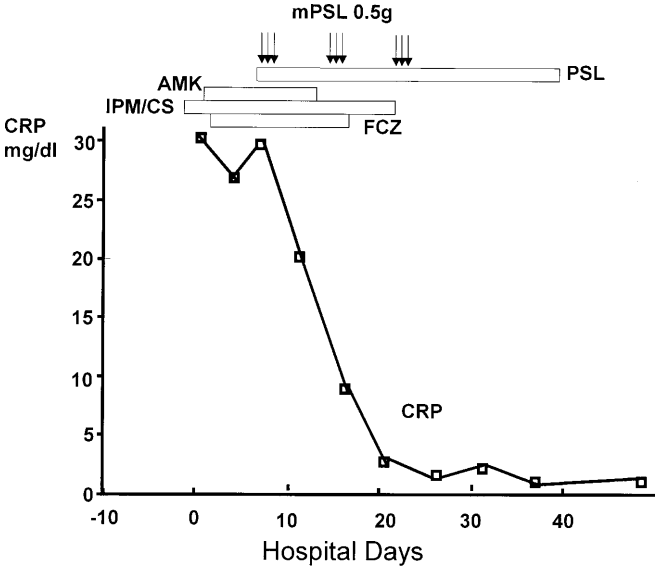

Fig. 4. Clinical course of case 2. *AMK*, amikacin

stools were not observed, which excluded the possibility of ischemic colitis. Cultures from blood, urine, and sputum were negative for infectious organisms. Several antibiotics and antifungal drugs were ineffective, and failed to improve her abdominal pain or CRP. A diagnosis of lupus pleuritis and peritonitis was made. Methylprednisolone pulse therapy was initiated with the same regimen as in case 1. Following this therapy, her clinical symptoms, including pleural and peritoneal effusion, subsided dramatically and CRP returned to normal levels (Fig. 4).

Discussion

We have presented the cases of two patients with acute lupus serositis and extremely high levels of CRP. Other serological parameters reflecting lupus activity (i.e., anti-DNA antibodies and complement levels) were suggestive of relatively quiescent diseases. These laboratory findings initially prompted us to make an extensive search for infection sites. However, there was no evidence of infection, and the administration of various antibiotics failed to improve CRP and other clinical manifestations. Methylprednisolone pulse therapy was administered to both patients for the immediate relief of life-threatening clinical symptoms (one with dyspnea, and the other with severe abdominal pain). Following this therapy, CRP levels returned to a normal range, along with a resolution of serositis. Thus, CRP was markedly elevated in the absence of infection in these cases, and constituted a useful serological marker for monitoring disease activity.

Many, but not all, patients with active SLE do not show a significant elevation of CRP levels, even though their erythrocyte sedimentation rate may be elevated.[4,5] In a prospective longitudinal study on 71 lupus patients, ter Borg et al.[6] demonstrated that median CRP levels during infection were significantly higher than those during disease exacerbation in lupus patients (6.0 vs. 1.65 mg/dl, respectively). In this regard, the measurement of CRP in SLE cases has been regarded as a valuable tool to distinguish between infection and exacerbation. However, they also noted that lupus serositis was associated with strong CRP responses whose levels were comparable to those during infection. The median level of CRP during exacerbation accompanied by serositis was 7.6 mg/dl, which was higher than that during exacerbation without serositis (1.6 mg/dl). As in our cases, 3 out of 13 serositis patients in their series had CRP levels exceeding 30 mg/dl even in the absence of infection. Thus, the CRP response in a subset of SLE patients may be different from that in others. However, because of a lack of large-scale studies of lupus serositis and CRP, the prevalence of the high CRP response among lupus serositis patients has not been clarified.

It is not known why a subset of SLE patients show strong CRP responses and others do not. It might be because serositis is a condition characterized by a large inflammatory cell mass, as compared with other lupus conditions.[7] IL6 is a cytokine which induces acute-phase proteins, including CRP. Spronk et al.[8] measured concentrations of IL6, IgG, anti-dsDNA antibodies, and CRP before and during exacerbation in patients with SLE. As expected, IL6 levels were well correlated with CRP levels but not with anti-dsDNA and IgG levels. It is of interest that increases in IL6 concentrations prior to exacerbation of SLE only occurred in a subgroup of patients characterized by serositis and elevated CRP levels during exacerbation. These finding suggests that IL6 may regulate a strong CRP response in lupus serositis patients. Unfortunately, however, we did not measure IL6 levels in our patients.

At autopsy, evidence of peritoneal inflammation has been found in approximately 60% of patients with SLE. However, only a minority (up to 11%) displayed symptomatic manifestation of serositis.[1] Although care must be taken to rule out infections, we should bear in mind the possibility of lupus serositis in any patient with SLE whose serum CRP levels are highly elevated. Alternatively, the measurement of CRP is invaluable to distinguish between infection and exacerbation among patients with lupus serositis.

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