Outcome of protein-losing gastroenteropathy in systemic lupus erythematosus treated with prednisolone and azathioprine

C. C. Mok, K. Y. Ying¹, A. Mak, C. H. To and M. L. Szeto

Objectives. To report the efficacy of prednisolone and azathioprine (AZA) in the treatment of systemic lupus erythematosus (SLE)-related protein-losing gastroenteropathy (PLGE).

Methods. Between 1995 and 2002, 16 consecutive Chinese patients with SLE-related PLGE were treated with a regimen consisting of high-dose prednisolone (0.8–1 mg/kg/day for 6 weeks, then tapered to ≤10 mg/day) and AZA (2 mg/kg/day). Protein leakage from the gastrointestinal tract was confirmed by 99mTc-labelled human serum albumin scintigraphy and significant urinary loss of protein was excluded. Clinical response at 6 months of therapy was assessed and patients were followed for relapse of PLGE.

Results. Clinical characteristics of our patients at the time of PLGE were: age 36.2 ± 8.7 (s.d.) yr; female: male ratio 15:1; mean SLE duration 29.6 ± 65 months. Twelve patients had PLGE as the initial presentation of SLE. Fifteen (94%) patients had concomitant activity in other organs. All patients presented with oedema and eight patients (50%) had non-bloody diarrhoea. The mean serum albumin level was 22.8 ± 5.7 g/dl. Protein leakage was at the small bowel in 11 (69%) patients and the large bowel in 5 (31%) patients. At 6 months of therapy, 14 (88%) patients had complete clinical response, 1 (6%) patient responded partially and 1 patient (6%) was treatment-refractory. Patients who responded were maintained on low-dose prednisolone (7.8 ± 6.1 mg/day) and AZA (56.3 ± 37 mg/day). Over a mean follow-up of 57.5 months, 1 (6%) patient had relapse of PLGE which responded to augmentation of prednisolone dosage. No patients developed alternative gastrointestinal diagnoses. Corticosteroid-induced psychosis, AZA-induced pancytopenia and herpes zoster occurred in three patients.

Conclusion. PLGE is an uncommon manifestation of SLE. Treatment with a combination of prednisolone and AZA is effective and well tolerated.

Key words: Gastrointestinal, Enteropathy, Therapy, Complications, Serositis.

Protein-losing gastroenteropathy (PLGE) is a condition characterized by hypoalbuminaemia secondary to excessive loss of serum protein from the gastrointestinal tract. It can be caused by a large number of gastrointestinal pathologies from the stomach down to the colon. Mechanisms of protein loss include mucosal injury with or without erosions/ulcerations, increase in mucosal permeability and loss of lymphatic fluid as a result of obstruction [1]. To establish a diagnosis of PLGE, in addition to the demonstration of protein loss from the gastrointestinal tract, significant loss of protein from other sources, such as the urinary tract, and reduced protein intake and synthesis due to malnutrition or severe liver diseases have to be excluded.

PLGE is a well reported but uncommon manifestation of systemic lupus erythematosus (SLE) [2–29]. Most previous reports involved isolated cases or small series of patients. The exact pathogenesis of PLGE in SLE remains elusive. Intestinal or mesenteric vasculitis is a likely mechanism [26] but is usually absent in mucosal biopsies. Other postulated mechanisms include mucosal disruption, increase in mucosal capillary permeability as a result of complement- or cytokine-mediated damage, ruptured mucosal lacteals and lymphangiectasia [5, 6, 14, 15]. Treatment of SLE-related PLGE has been heterogeneous and anecdotal. Most previously reported cases responded to corticosteroid treatment. However, the optimal therapy is virtually unknown as there have not been any controlled clinical trials in this condition.

Here we report our experience on the treatment of SLE-related PLGE with a combination of prednisolone and azathioprine. Comparison is made with 32 other cases of SLE-related PLGE reported in the English literature.

Patients and methods

Between 1995 and 2002, 16 consecutive Chinese patients with SLE-related PLGE diagnosed at Tuen Mun and Princess Margaret Hospitals (Hong Kong) were treated with a regimen consisting of oral prednisolone (0.8–1 mg/kg/day for 6 weeks, then tapered by 5 mg/week until ≤10 mg/day) and azathioprine (AZA) (started at 1 mg/kg/day and targeted to 2 mg/kg/day). All patients fulfilled at least four of the American College of Rheumatology (ACR) criteria for the classification of SLE [30]. Once a clinical response had been achieved, patients were maintained on low-dose prednisolone (5–10 mg/day) and AZA (1–2 mg/kg/day) indefinitely. Informed consent was obtained from patients regarding the current treatment regimen.

Protein leakage from the gastrointestinal tract in our patients was confirmed by technetium 99m-labelled human serum albumin scanning. Significant loss of protein from the urinary tract was excluded by urinary protein quantification. Malnutrition states and severe liver diseases were excluded by using the history, physical examination and preliminary blood tests.
Upper endoscopies were routinely performed for all patients. Colonoscopies were performed for patients with albumin scanning, showing protein leakage at the large bowel or when there was persistent diarrhoea. Contrast computed tomography (CT) scans of the abdomen and further investigations into small bowel pathologies were performed depending on the level of clinical suspicion. Serial data on serum albumin, complement levels and SLE activity were obtained. Clinical response at 6 months of prednisolone and AZA therapy was assessed. Patients were followed for clinical relapse of PLGE and alternative diagnoses that might have accounted for the protein loss.

Assessment of clinical response

Complete response of PGLE was defined as complete resolution of oedema and gastrointestinal symptoms, together with return of the serum albumin level to ≥35 g/dl (the lower limit of the normal range) and improvement of the C3 level for at least 3 months. Partial response referred to a partial improvement of oedema and gastrointestinal symptoms, which was associated with an improvement of serum albumin not to the extent of complete response (but ≥30 g/dl), and an improvement in C3 level for ≥3 months. Non-response (treatment refractoriness) was defined as persistent or deteriorating clinical symptoms, and/or failure of serum albumin to increase to 30 g/dl or more.

Assessment of disease activity of SLE

Disease activity of SLE was measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), a validated tool which has been shown to be sensitive to change [31]. The SLEDAI scores before and 6 months after treatment were compared.

Statistical analyses

Data were expressed as mean ± s.d. Changes in various biochemical parameters before and after treatment were compared by paired Students’ t-test and Wilcoxon’s matched pairs analysis for continuous and categorical data, respectively. Comparison between two groups was made by the independent Students’ t-test and the χ² test for continuous and categorical variables, respectively. Statistical significance was defined as a P value of less than 0.05, two-tailed. All statistical analyses were performed using the SPSS program, version 11.5 (SPSS, Chicago, IL, USA) for Windows XP.

Results

The clinical characteristics of our 16 patients at the time of PLGE were as follows: age 36.2 ± 8.7 yr; female:male ratio 15:1; SLE duration 29.6 ± 65 months. Twelve (75%) patients had PLGE as the initial presentation of SLE. Fifteen (94%) patients had concomitant disease activity in other organs (summarized in Table 1). The mean SLEDAI score was 14.3 ± 7.2. Anti-double-stranded DNA (dsDNA) and anti-extractable nuclear antigen (ENA) antibodies were found in 12 (75%) and 12 (75%) patients, respectively. Fifteen (94%) patients had hypocoomplementemia at the presentation of PLGE.

All patients with PLGE presented with either generalized or dependent oedema. Gastrointestinal symptoms (diarrhoea, abdominal pain, nausea, vomiting or anorexia) occurred in 12 (75%) patients. Among these, non-bloody diarrhoea was the presenting symptom in eight (50%) patients. The mean serum albumin level was 22.8 ± 5.7 g/dl and hypoalbuminaemia could not be accounted for by the degree of proteinuria (mean 0.61 ± 0.45 g/day) or reduced oral intake. Anaemia (haemoglobin level, ≤10 g/dl) was found in 10 (63%) patients at presentation of PGLE. Three patients had mild elevation of the parenchymal liver enzymes (less than 3 times the upper normal limit) but none had evidence of chronic liver disease. Cardiac problems, such as congestive heart failure or constrictive pericarditis, were not present in any of the patients.

Table 1. Concomitant organ manifestations of our SLE patients at presentation of protein-losing gastroenteropathy

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Arthritis</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Malar erythema</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Discoid skin lesions</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Oral ulceration</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Fever</td>
<td>12 (75)</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Cutaneous vasculitis</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Neuropsychiatric disease</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Iliaculcer</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0 (0)</td>
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*Renal biopsy in one patient showed mesangial proliferative nephritis; biopsy not performed in others because of the mild degree of proteinuria.

99mTc-labelled human serum albumin scan documented protein leakage at the small bowel in 11 (69%) patients and the large bowel in 5 (31%) patients. Figure 1 shows the typical appearance of the albumin scans in a SLE patient with protein loss at the large bowel. Upper endoscopies in all patients and colonoscopies in nine patients (before immunosuppressive treatment) did not reveal significant lesions. Mild mucosal oedema was reported in two patients, and mucosal biopsies in five patients did not show any specific histological abnormalities, including inflammatory infiltrates. Barium meal and follow-through examination performed in seven patients did not demonstrate any focal lesions. Malabsorption studies, including jejunal biopsy, were normal in two patients.

For patients who presented with gastrointestinal symptoms, stools were negative for ova and parasites, and bacterial cultures were unrevealing. Ultrasonography of the abdomen in 10 patients did not show any significant abnormalities. Contrast CT scanning of the abdomen was performed in four patients: all revealed ascites, one showed small bowel thickening and one showed mesenteric lymphadenopathy. Ascites, documented by clinical examination, ultrasonography or CT scanning, was reported in eight (50%) patients. Seven (44%) patients had associated pleural or pericardial effusion.

All patients were treated initially with oral prednisolone (mean dose 43.8 ± 15 mg/day) and AZA (mean dose 71.6 ± 31 mg/day). At 6 months of therapy, 14 (88%) patients had complete clinical and serological response, 1 (6%) patient responded partially and 1 patient (6%) was treatment-refractory (but subsequently responded to intravenous pulse cyclophosphamide). Table 2 shows the changes in haemoglobin, serum albumin and complement levels and SLEDAI scores during the first 6 months of treatment. Significant improvement in all these parameters was demonstrated in our patients.

Patients with clinical response were maintained on low-dose prednisolone (7.8 ± 6.1 mg/day) and AZA (56.3 ± 37 mg/day). Over a mean follow-up of 57.5 months, one (6%) patient had relapse of PLGE which responded to augmentation of prednisolone dosage. None of the patients developed alternative gastrointestinal diagnoses, such as chronic infection, malignancy and malabsorption syndromes, that might have accounted for the hypalbuminaemia.
Regarding adverse events, corticosteroid-induced psychosis, AZA-induced pancytopenia and herpes zoster occurred in three patients (one for each event). Major infective episodes leading to hospitalization were not reported. One patient died of severe pulmonary hypertension, which was unrelated to her gastrointestinal problem.

Comparison with other patients reported in the literature

Table 3 shows the clinical characteristics and initial immunosuppressive treatment of our patients in comparison with 32 other cases reported in the literature [2–29]. The age and gender distributions of the two groups were similar. Eighteen (56%) patients in the literature were Asians (mostly Japanese) and in most circumstances, PLGE was the initial presentation or preceded the presentation of full-blown SLE. Non-bloody diarrhoea was present in 38% of the reported patients, a figure close to what we observed in our patients.

Specific endoscopic or histological findings were absent in most cases reported in the literature. The commonest endoscopic appearance was mucosal oedema. Biopsy was often normal or revealed non-specific findings such as villous oedema, dilated lacteals or inflammatory infiltrates. Definite lymphangiectasia, vasculitis or C3 deposition in the capillary walls of the lamina propriae of villi is described in only a few reports [14, 15, 26]. Most patients in the literature were treated initially with

![Image](http://rheumatology.oxfordjournals.org/doi/fig/10.1093/rheumatology/ket137)
corticosteroids (97%). AZA was used in conjunction in five patients [7, 10, 15, 18, 19]. Cyclophosphamide was used in five patients (three corticosteroid-refractory patients, and for nephritis in one patient) [3, 5, 13, 16, 25]. All except four (88%) patients responded to corticosteroid therapy. Of 13 patients with a follow-up for more than 12 months, four (31%) had a relapse of PLGE, which occurred in three (75%) patients while they were receiving low-dose prednisolone alone as maintenance therapy [7, 18, 22, 27]. In contrast, no relapse of PLGE was described in four patients who were maintained on low-dose prednisolone and AZA [3, 7, 15, 19]. One of these patients had relapse of PLGE when prednisolone and AZA were discontinued [7].

**Discussion**

This was an open-label study of the efficacy of a combination of oral prednisolone and AZA in the treatment of PLGE in patients with SLE. Our experience indicates that this regimen is associated with a high response rate, which occurs in the first few months of therapy. Extra-gastrointestinal SLE disease activity also improves significantly. With maintenance therapy using low-dose prednisolone and AZA, clinical relapse of PLGE is uncommon. Moreover, treatment is generally well tolerated with no major infective complications reported.

PLGE is an uncommon manifestation of SLE. Hitherto, fewer than 40 cases have been reported in the literature. Of the patients [2–29] summarized in this paper, more than half were Asians, indicating that this manifestation of SLE may be more common in Oriental patients. Whether this is due to genetic or environmental factors remains to be elucidated. Within the specified period in our study, 498 SLE patients attended the rheumatology and lupus clinics of the participating hospitals, giving a point prevalence of 3.2% for PLGE in our Chinese SLE population. This figure may possibly be an underestimate because routine screening of protein leakage from the gastrointestinal tract is not performed unless this is a clinical indication for unexplained hypoalbuminaemia.

As shown in our study and the cases reported in the literature, PLGE may occur in SLE patients of any age. The skewed gender distribution is in keeping with the female preponderance of SLE itself. In three-quarters of the patients, symptoms of PLGE occur some time before or during the diagnosis of SLE. In most circumstances, the more typical features of SLE develop only after presentation of PLGE. No particular autoantibodies have been found to be associated with PLGE in patients with SLE. As shown in our series, the prevalences of anti-dsDNA and anti-ENA antibodies are not impressively different from those in other SLE patients without this manifestation.

The exact pathogenesis of SLE-related PLGE is still unclear. Mucosal ulceration, vasculitis, increase in capillary permeability, cytokine- or complement-mediated vascular or mucosal damage, and lymphatic dilatation have been postulated but are difficult to demonstrate histologically. Diagnosis of SLE-related PLGE mainly relies on exclusion of other gastrointestinal pathologies that may account for the protein loss. The good clinical response of our patients to immunosuppressive treatment and the absence of alternative diagnoses on follow-up suggest that PLGE is probably related to disease activity of SLE. Although the presence of hypocomplementaemia in most of our patients may suggest an immune complex-mediated mechanism, this might also be related to concomitant disease activity in other organs.

Because of the lack of controlled trials, treatment of SLE-related PLGE is purely anecdotal. The response to corticosteroid is generally excellent, as shown in our series of patients and in those reported in the literature. Not much information on the relapse rate in PLGE can be derived from historical cases because most reports just concentrate on the short-term treatment response. It appears that relapse of PLGE is more common in patients receiving maintenance therapy with low-dose prednisolone alone than in those receiving a combination of prednisolone and AZA. Consistently with this, our experience suggests that relapse of PLGE is uncommon with long-term maintenance treatment consisting of low-dose prednisolone and AZA. However, whether the long-term efficacy of combining corticosteroid and AZA is better than that of corticosteroid alone in the treatment of SLE-related PLGE has to be established by further randomized controlled trials. In view of the good response of SLE-related PLGE to combined prednisolone and AZA treatment, more aggressive approaches, such as the use of cyclophosphamide, should be reserved for those with recalcitrant disease. Prophylaxis for thromboembolic complications should be considered in patients with severe and persistent protein loss, especially if antiphospholipid antibodies are present.

In summary, PLGE is an uncommon manifestation of SLE and is usually associated with disease activity in other organs. Initial treatment with a combination of prednisolone and AZA leads to significant improvement in both gastrointestinal and extra-gastrointestinal disease activity. With maintenance therapy, relapse of PLGE is infrequent. Treatment is generally well tolerated. However, whether the prednisolone–AZA combination is better than prednisolone alone in reducing relapses of lupus-related PLGE has to be explored in future controlled trials.

The authors have declared no conflicts of interest.

**References**

13. Meulemans Q, Michel C, Marteau P et al. Association of chronic interstitial cystitis, protein-losing enteropathy and paralytic ileus with...


