Case Report

Concomitant lupus nephritis and bullous eruption in systemic lupus erythematosus

Yee Yung Ng, I. Ter Chang, Tzen Wen Chen, Han Nang Liou, An Hang Yang and Wu Chang Yang

Division of Nephrology, Department of Medicine, Department of Dermatology and Department of Pathology, Veterans General Hospital-Taipei, National Yang Ming University, Taipei, Taiwan, Republic of China

Introduction

Most patients with systemic lupus erythematosus (SLE) develop cutaneous manifestations such as malar rashes, painless oral ulcers, discoid skin lesions and photosensitivity. The development of a generalized vesicobullous eruption is rare [1–3]. A bullous eruption with distinct clinical and immunopathological features associated with SLE has been described as bullous SLE, bullous eruption of SLE or SLE with vesicobullous lesions [4–6]. We observed a case of bullous SLE in a close temporal relationship with lupus nephritis; both abnormalities responded to glucocorticoid therapy and plasmapheresis.

Case

This 47-year-old man was in good health until April 1996. He suffered from malar rashes and photosensitivity for 1 month. At that time, C₃ and C₄ were 95 mg/dl (normal, 80–155 mg/dl) and 39.7 mg/dl (normal, 13–37 mg/dl), respectively. Double-stranded DNA (dsDNA) was 10 IU/ml (normal, <10 IU/ml). A skin biopsy showed lupus erythematosus profundus. He was then transferred in May to our dermatology ward following MTP pulse therapy. Oral prednisolone 60 mg and azathioprine (100 mg per day) were administered for 1 month. At that time, C₃ and C₄ were 51 and 20 mg/dl, respectively. The complete blood count (CBC) was within the normal range. The serum creatinine and urea concentrations were 1.3 mg/dl (normal, 0.5–1.5 mg/dl) and 20 mg/dl (normal, 8–20 mg/dl), respectively. Immunological profiles disclosed IgG 860 mg/dl (normal, 700–1600 mg/dl), IgA 261 mg/dl (normal, 70–400 mg/dl), IgM 68 mg/dl (normal, 40–230 mg/dl), C₃ 32 mg/dl (normal, 80–155 mg/dl), C₄ <7.6 mg/dl (normal, 13–37 mg/dl) and dsDNA 32 IU/ml (normal, <10 IU/ml). Proteinuria (>300 mg/dl) and microhaematuria (RBC eruptions (Table 1)) were noted on urinalysis. A renal fine-needle biopsy was performed. Light microscopy (LM) demonstrated focal glomerulonephritis, and electronic microscopy (EM) confirmed the existence of subendothelial/mesangial electron-dense deposition with characteristic fingerprints, compatible with the diagnosis of lupus nephritis class III (Figure 1A and B).

Unfortunately, fulminant vesicobullous eruptions over the trunk and extremities developed within 2 days (Figure 2A). Methylprednisolone (MTP) pulse therapy (1 g per day) was prescribed on four consecutive days, because dapsone was not available when the vesicobullous lesions became widespread. During the vesicobullous eruptions, there was no fever. The white blood cell count was 7800/mm³ with 4.5% eosinophils. Aspiration cytology obtained from bullae showed abundant neutrophils and no lymphocytes. The bullous fluid was sterile on bacterial culture. The Tzanck smear was negative for virally infected keratinocytes. The skin biopsy of the vesicobullous eruptions disclosed a subepidermal blister with diffuse band-like neutrophilic infiltration of the upper dermis, compatible with bullous SLE (Figure 3A and B). Because of the persistent vesicobullous eruption, five plasma exchanges were made on alternative days following the MTP pulse therapy. Oral prednisolone 60 mg and cyclophosphamide 100 mg per day were administered following MTP pulse therapy. The clinical condition improved and the patient was discharged with non-scarring skin (Figure 2B). One month later, he was admitted for MTP pulse therapy due to recurrent vesicobullous eruptions starting from both knees. Serum creatinine and urea concentrations were 1.1 and 32 mg/dl, respectively. C₃ and C₄ were 51 and 9.9 mg/dl, respectively. These blisters were suppressed with subsequent MTP administration, and healed without leaving scars. In view of persistent proteinuria, microhaematuria and recurrent vesicobullous eruptions (Table 1), cyclosporin (125 mg per day) was added to azathioprine (100 mg per day) and prednisolone (60 mg per day) after completion of the MTP pulse therapy. Proteinuria and lupus activity indices including dsDNA, C₃ and C₄ were improved after medication (Table 1).

Three months later, a repeat renal biopsy was performed with 4.5% eosinophils. Aspiration cytology obtained from bullae showed abundant neutrophils and no lymphocytes. The Tzanck smear was negative for virally infected keratinocytes. The skin biopsy of the vesicobullous eruptions disclosed a subepidermal blister with diffuse band-like neutrophilic infiltration of the upper dermis, compatible with bullous SLE (Figure 3A and B). Because of the persistent vesicobullous eruption, five plasma exchanges were made on alternative days following the MTP pulse therapy. Oral prednisolone 60 mg and cyclophosphamide 100 mg per day were administered following MTP pulse therapy. The clinical condition improved and the patient was discharged with non-scarring skin (Figure 2B). One month later, he was admitted for MTP pulse therapy due to recurrent vesicobullous eruptions starting from both knees. Serum creatinine and urea concentrations were 1.1 and 32 mg/dl, respectively. C₃ and C₄ were 51 and 9.9 mg/dl, respectively. These blisters were suppressed with subsequent MTP administration, and healed without leaving scars. In view of persistent proteinuria, microhaematuria and recurrent vesicobullous eruptions (Table 1), cyclosporin (125 mg per day) was added to azathioprine (100 mg per day) and prednisolone (60 mg per day) after completion of the MTP pulse therapy. Proteinuria and lupus activity indices including dsDNA, C₃ and C₄ were improved after medication (Table 1).

Three months later, a repeat renal biopsy was performed.
Fig. 1. The first renal biopsy under electron microscopy showed (A) subendothelial/mesangial electron-dense depositions (3760 ×) (arrow) with (B) a characteristic fingerprint (7520 ×). (C) After appropriate treatment, the repeated renal biopsy showed subepithelial electron-dense depositions (3760 ×).
<table>
<thead>
<tr>
<th>Date</th>
<th>Bullous</th>
<th>BUN (mg/dl)</th>
<th>Cr (mg/dl)</th>
<th>24-h UP (gm/day)</th>
<th>C₁ (mg/dl)</th>
<th>C₄ (mg/dl)</th>
<th>DaDNA (IU/ml)</th>
<th>PDN (mg/day)</th>
<th>MTP (1 g/day)</th>
<th>CPM (mg/day)</th>
<th>AZP (mg/day)</th>
<th>CSA (mg/day)</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/06/96</td>
<td>–</td>
<td>20</td>
<td>1.3</td>
<td>2.24</td>
<td>95</td>
<td>39.7</td>
<td>10</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>05/19/96</td>
<td>+</td>
<td>35</td>
<td>1.5</td>
<td>2.25</td>
<td>31</td>
<td>&lt;7.6</td>
<td>32</td>
<td>60</td>
<td>×4 days</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>05/23/96</td>
<td>+</td>
<td>39</td>
<td>1.4</td>
<td>ND</td>
<td>32</td>
<td>&lt;7.6</td>
<td>ND</td>
<td>60</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>×5 times</td>
</tr>
<tr>
<td>06/02/96</td>
<td>–</td>
<td>37</td>
<td>1.4</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>60</td>
<td>–</td>
<td>100</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>05/16/97</td>
<td>–</td>
<td>21</td>
<td>1.2</td>
<td>ND</td>
<td>52</td>
<td>ND</td>
<td>62.2</td>
<td>10</td>
<td>5</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>05/31/98</td>
<td>–</td>
<td>23</td>
<td>1.3</td>
<td>1.2</td>
<td>43.5</td>
<td>15.3</td>
<td>ND</td>
<td>15</td>
<td>–</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>06/03/98</td>
<td>–</td>
<td>22</td>
<td>1.4</td>
<td>3.68</td>
<td>72.5</td>
<td>29.5</td>
<td>ND</td>
<td>10</td>
<td>–</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>06/28/96</td>
<td>–</td>
<td>32</td>
<td>1.1</td>
<td>7.17</td>
<td>51</td>
<td>9.9</td>
<td>10.04</td>
<td>60</td>
<td>×3 days</td>
<td>100</td>
<td>100</td>
<td>125</td>
<td>–</td>
</tr>
<tr>
<td>07/12/96</td>
<td>–</td>
<td>38</td>
<td>1.3</td>
<td>6.89</td>
<td>43.5</td>
<td>&lt;10</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>07/18/96</td>
<td>–</td>
<td>28</td>
<td>1.2</td>
<td>7.22</td>
<td>52</td>
<td>19.1</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>07/30/96</td>
<td>–</td>
<td>36</td>
<td>1.5</td>
<td>6.5</td>
<td>62.2</td>
<td>31.8</td>
<td>10</td>
<td>40</td>
<td>–</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>08/23/96</td>
<td>–</td>
<td>28</td>
<td>1.3</td>
<td>7.33</td>
<td>62.2</td>
<td>51.8</td>
<td>10</td>
<td>30</td>
<td>–</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>09/06/96</td>
<td>–</td>
<td>30</td>
<td>1.4</td>
<td>3.48</td>
<td>66.9</td>
<td>31.5</td>
<td>&lt;10</td>
<td>25</td>
<td>–</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>09/24/96</td>
<td>–</td>
<td>22</td>
<td>1.4</td>
<td>3.68</td>
<td>72.5</td>
<td>29.5</td>
<td>ND</td>
<td>15</td>
<td>–</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10/18/96</td>
<td>–</td>
<td>30</td>
<td>1.2</td>
<td>2.43</td>
<td>82.9</td>
<td>34.8</td>
<td>&lt;10</td>
<td>10</td>
<td>–</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>12/27/96</td>
<td>–</td>
<td>21</td>
<td>1.2</td>
<td>0.78</td>
<td>96</td>
<td>22</td>
<td>&lt;5.8</td>
<td>5</td>
<td>–</td>
<td>100</td>
<td>125</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>12/27/96</td>
<td>–</td>
<td>21</td>
<td>1.2</td>
<td>1.17</td>
<td>73.8</td>
<td>34.8</td>
<td>&lt;4.53</td>
<td>5</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>01/02/97</td>
<td>–</td>
<td>24</td>
<td>1.2</td>
<td>0.57</td>
<td>63</td>
<td>14.7</td>
<td>&lt;4.60</td>
<td>5</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>01/05/97</td>
<td>–</td>
<td>24</td>
<td>1.2</td>
<td>0.34</td>
<td>67</td>
<td>16.3</td>
<td>&lt;4.20</td>
<td>5</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>01/14/97</td>
<td>–</td>
<td>24</td>
<td>1.2</td>
<td>1.03</td>
<td>44</td>
<td>18.9</td>
<td>&lt;10</td>
<td>5</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>02/03/97</td>
<td>–</td>
<td>23</td>
<td>1.4</td>
<td>0.62</td>
<td>48.7</td>
<td>19.6</td>
<td>&lt;10</td>
<td>15</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>02/10/97</td>
<td>–</td>
<td>21</td>
<td>1.4</td>
<td>0.87</td>
<td>46.1</td>
<td>16.8</td>
<td>&lt;10</td>
<td>15</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>03/03/97</td>
<td>–</td>
<td>24</td>
<td>1.3</td>
<td>0.69</td>
<td>46.1</td>
<td>15.5</td>
<td>&lt;10</td>
<td>10</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>03/12/97</td>
<td>–</td>
<td>21</td>
<td>1.4</td>
<td>0.62</td>
<td>48.7</td>
<td>19.6</td>
<td>&lt;10</td>
<td>15</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>03/19/98</td>
<td>–</td>
<td>22</td>
<td>1.4</td>
<td>0.87</td>
<td>46.1</td>
<td>16.8</td>
<td>&lt;10</td>
<td>15</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>04/09/98</td>
<td>–</td>
<td>23</td>
<td>1.3</td>
<td>0.65</td>
<td>67</td>
<td>14.4</td>
<td>&lt;5</td>
<td>12.5</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

24 h UP, 24 h urinary protein; dsDNA, double-stranded DNA; PDN, prednisolone; MTP, methylprednisolone; CPM, cyclophosphamide; AZP, azathioprine; CSA, cyclosporin; PE, plasma exchange.

Normal range: C₁ 80–155 mg/dl, C₄ 13–37 mg/dl, dsDNA <10 U/ml.
performed in order to evaluate the relationship between bullae regression and the pathological findings of nephritis. The LM study showed membranous glomerulopathy, and the EM study demonstrated global subepithelial electron-dense deposition with spike formation, compatible with lupus nephritis, class V (Figure 1C). At the last follow-up at 30 months, cyclosporin was discontinued, and immunosuppressive agents were tapered (Table 1).

Discussion

Blistering eruptions are rare in SLE. Clinically, one has to exclude other primary bullous diseases such as epidermolysis bullosa acquisita (EBA), dermatitis herpetiformis (DH) or bullous pemphigoid (BP). Among these blistering disorders, bullous SLE is a distinct disease entity fulfilling the revised criteria of the American Rheumatism Association (ARA) of 1982: a chronic, widespread, non-scarring blistering eruption, characterized by subepidermal blisters with acute predominantly neutrophilic inflammation in the upper dermis, immune complex deposition at the basement membrane by immunofluorescence, and immune deposits beneath the lamina densa by ultrastructural analysis [7,8]. In this case, the skin biopsy disclosed a subepidermal blister with diffuse band-like neutrophils infiltrating over the upper dermis, compatible with bullous SLE. Although immunofluorescence and EM evaluation of the skin was not performed in this case, recovery without scar formation further supports the diagnosis.

There is controversy about the relationship between blistering and renal involvement. Some authors have stated that blistering does not coincide with the activity of systemic disease [9], but this was not noted by Shirahama and Burrows [3,10]. In our case, two episodes of vesicobullous eruptions occurred at a time of high lupus activity (C4 <10 mg/dl) (Table 1), but not while lupus activity was low during the last 30 months of follow-up, suggesting that the activity of blistering is a sign of disease flare [3,10]. Although Janniger et al. reported one renal histology in a bullous SLE patient [11], the specimen demonstrating proliferative nephritis was obtained 5 years after blistering.

**Fig. 2.** (A) Vesicobullous eruptions over the lower limbs, (B) healing without scarring.

**Fig. 3.** (A) A subepidermal blister (100 ×) (arrow). (B) In the upper dermis, a diffuse band-like dense inflammatory infiltrate is seen beneath the base of the blister, mainly composed of neutrophils (400 ×).
before vesicobullous eruption occurred. Our patient is apparently the first case illustrating the simultaneous occurrence of biopsy-proven lupus nephritis with bullous SLE. EM revealed the transformation from type III to type V within 3 months (Figure 1A and C). Is regression of the bullae paralleled by transformation of renal histology? Further cases may be needed to answer this question.

Although dapsone was reported as the drug of choice for bullous SLE [9,12], MTP instead of dapsone was administered in our case. Because of the progressive vesicobullous lesion, high lupus activity (C3 32 mg/dl, C4 < 7.6 mg/dl, dsDNA 32 IU/ml) and renal involvement (proteinuria), cyclophosphamide and plasma exchange were added after MTP pulse therapy and, because of the recurrence of vesicobullous eruptions, cyclosporin (125 mg per day) was added.

Bullous eruptions in SLE are rare. The parallel improvement of cutaneous and renal involvement suggests that vesicobullous lesions are a sign of disease flare.

References


Downloaded for guest on 12 April 2019