Prevalence, patterns of disease and outcome in patients with systemic lupus erythematosus who develop severe haematological problems

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Objective. To evaluate the prevalence of major haemolytic disease—severe autoimmune haemolytic anaemia and severe thrombocytopenia—and to assess when these features develop. We also sought to analyse the clinical and serological outcomes of patients with haemolytic anaemia and thrombocytopenia with systemic lupus erythematosus (SLE) as compared with patients without these cytopenias.

Methods. We reviewed retrospectively all the available case notes from our lupus cohort of 305 patients followed up between 1978 and 2000 (mean follow-up 7 yr). We identified 30 patients with SLE (9.8%), of whom 20 (6.6%) had severe haemolytic anaemia and 10 (3.3%) had severe thrombocytopenia. Each patient was matched for age, sex and ethnicity with two control patients.

Results. We recorded a total of 42 episodes of severe haematological events: four patients had a second haemolytic episode and eight patients had a second thrombocytopenic episode. Five patients had both thrombocytopenia and haemolytic anaemia. One per cent of patients had severe haemolytic anaemia prior to the diagnosis of SLE and 2.5% of patients presented with these haematological disorders. Haemolytic anaemia and thrombocytopenia were associated with renal involvement (0.01 > P > 0.001) and anticardiolipin antibodies (ACL) (0.01 > P > 0.001), but not anti-dsDNA antibodies. Calculation of the BILAG index at the time of severe haematological crisis demonstrated that renal, central nervous system involvement and general symptoms are more frequently present. Forty-one per cent of patients were already on either prednisolone (< 10 mg) or an immunosuppressive agent at the onset of the event.

Conclusion. Our data demonstrate that both haemolytic anaemia and thrombocytopenia are associated with ACL but not anti-dsDNA antibodies. When faced with a patient with a severe haematological manifestation of lupus, active disease in other organs is likely to be present.

Keywords: SLE, Autoimmune haemolytic anaemia, Thrombocytopenia.

Anaemia and thrombocytopenia are common features of systemic lupus erythematosus (SLE), but the prevalence of the severe forms of these haematological disorders is not well established. It has been shown previously that autoimmune haemolytic anaemia occurs in approximately 5–10% of patients with SLE [1–4]. Although thrombocytopenia caused by peripheral immune destruction is common in SLE (20–40%), severe thrombocytopenia is comparatively rare (~5%) and can pre-date other features of SLE [5]. We determined when these features developed during the course of the disease in a cohort that has been followed

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up in a single centre with a low drop-out rate (for reasons other than death) over a 20-yr period.

We assessed if there was an association of disease activity as determined by the British Isles Lupus Assessment Group (BILAG) index [6] with disease activity in other systems. We also evaluated the clinical and serological associations in patients with SLE and haemolytic anaemia and thrombocytopenia when compared with those patients with lupus without these severe haematological disorders, to determine whether there were any other distinguishing features.

Patients and methods

All available case notes from our cohort of 305 patients (286 female, 19 male) with SLE were reviewed. This group consisted of 213 Caucasian, 47 Afro-Caribbean, 30 Asian, eight Chinese and 11 patients of other or mixed ethnic origin. All patients fulfilled the revised criteria for the diagnosis of SLE [7]. We considered severe haemolytic anaemia to be present when the haemoglobin was <8 g/dl, in the presence of a positive Coombs' test, a raised reticulocyte count and when the haemoglobin had dropped by 3 g/dl since the previous reading. We considered severe thrombocytopenia to be present when the platelet count was <50 × 10^9/l. We excluded other causes of anaemia including blood loss from the gastrointestinal tract, and other causes of haemolysis and thrombocytopenia including drug-induced and microangiopathic haemolytic anaemia. We determined the prevalence of these haemocytopenias and when these features developed during the course of the disease over a mean follow-up period of 7 yr.

Disease activity was recorded at the time of the acute haematological presentation using the BILAG index, which has been validated and shown to be reproducible and reliable [6]. The index allocates separate scores to each of eight organ-based systems (a total score is not calculated).

We further studied the association of haemolytic anaemia and thrombocytopenia with antiphospholipid antibodies (lupus anticoagulant assessed by the Russell viper venom test or IgG/IgM anticardiolipin antibodies measured by ELISA, n < 5 GpLu/MpLu, Shield Diagnostics Dundee) and anti-dsDNA antibodies (Shield Diagnostics Dundee, n < 50 U/ml). We also looked at the clinical outcome over the course of the disease focusing on: serositis, joint involvement, alopecia, central nervous system (CNS) events, renal involvement (confirmed on biopsy) and death in the study group. This group was then compared with controls matched for age, sex and ethnicity and to the SLE cohort as a whole. Two controls were matched for each study patient for age, sex, ethnicity and to the SLE cohort as a whole. The index allocates separate scores to each of eight organ-based systems (a total score is not calculated).

We also analysed the treatment of the patients at the time of the diagnosis of haemolytic anaemia or thrombocytopenia and subsequent management of their disease (including treatment with prednisolone, immunosuppressant agents, i.v. immunoglobulin therapy and splenectomy).

Statistics

The χ²-test was used to compare dichotomous characteristics. Comparison of cases with controls was performed with the Wilcoxon test for matched pairs, P values < 0.05 were considered significant.

Results

Thirty patients with severe cytopenias were identified from a cohort of 305 patients. Twenty patients had severe thrombocytopenia and 10 patients had severe haemolytic anaemia (Table 1). We also identified 31 patients with mild thrombocytopenia, defined as a platelet count between 50 and 100 × 10^9, and six patients with mild haemolytic anaemia, defined as a haemoglobin level between 8 and 10 g/dl. However we chose to focus on the severe end of the spectrum of these haematological disorders, as it is these patients who require aggressive management. We recorded a total of 42 episodes of severe cytopenia, four patients had a second haemolytic episode and eight patients had a second thrombocytopenic episode. Five patients had both thrombocytopenia and haemolytic anaemia.

Table 1. Haematological events in patients with SLE

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Severe</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>No. of episodes</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>6</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>44</td>
<td>30</td>
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There was no association with renal failure. We also looked at manifestations such as alopecia, joint involvement, serositis, renal transplant, death from renal disease and death from all causes, but there was no significant difference between lupus patients with these haematological disorders and those without in any of these features.

At the time of the haematological event we also looked at the BILAG score in other organ systems. Figure 2 demonstrates the number of patients who had a score of A or B. Category A denotes disease thought to be sufficiently active to require disease-modifying treatment (prednisolone at >20 mg daily or immunosuppressants). Category B denotes disease which is less active than in ‘A’; mild reversible problems requiring only symptomatic therapy such as antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs) or prednisolone at <20 mg/day. Category C indicates stable mild disease [6]. In general it appears that renal disease, CNS involvement and general symptoms appear more frequently associated with active haematological disorders. No link to lymphopenia (present in 77% of our patients) was discernable and we do not have a measurement of anti-neuronal or anti-lymphocytotoxic antibodies available for comparison.

We also looked at the treatment at the time of diagnosis and subsequent management. Interestingly, 41% of patients were already on prednisolone at <10 mg/day at the occurrence of these cytopenias (Table 2).
Discussion

This study demonstrates that 10% of patients with SLE will have a severe haematological crisis at some point during the course of their disease (6.6% haemolytic anaemia and 3.3% thrombocytopenia) and a further 10% will have a mild haematological disturbance requiring close follow-up. Kokori et al. [1] identified 11.6% of patients with haemolytic anaemia over a follow-up period of 4 yr, whereas others have given a prevalence of 3.3% for haemolytic anaemia and 9.5 for autoimmune thrombocytopenia [8].

Very few authors have focused on very severe cases of haemolytic anaemia, although more attention has been paid to more profound thrombocytopenia (reviewed in [9]). We had anticipated that major haematological disease would have been linked to severe disease in other organs/systems. As we now report (see Fig. 2), using the BILAG disease activity score, we did find that patients with severe haematological disease were more likely to have significant disease in the renal, central nervous and general systems, but not in the other organs/systems.

In general 3–16% of patients with idiopathic thrombocytopenic purpura (ITP) may go on to develop SLE up to 10 yr after diagnosis [10]; 2.6% of the patients in our cohort presented with severe thrombocytopenia and 2.3% with severe haemolytic anaemia. We also found that a significant proportion of patients had their haematological crisis at diagnosis or within the first year of diagnosis of SLE (Fig. 1). This has also been demonstrated by others [1, 5].

We also demonstrated that patients with both haemolytic anaemia and thrombocytopenia have a significant association with ACL antibodies. IgG ACL antibodies have been associated with thrombocytopenia in patients with SLE [3]. Others have also shown this association with haemolytic anaemia [1, 10, 11]. There does, however, remain a controversy as to the importance of the two subtypes of anticardiolipin antibodies. In fact it has been shown that subtypes of both IgG and IgM are present in higher titres in idiopathic haemolytic anaemia than in normal controls irrespective of underlying SLE [12] and patients with haemolytic anaemia were more likely to have IgG anticardiolipin antibodies than controls [1]. Deleze et al. [3] and Cervera et al. [13] have reported strong associations with IgM and others have suggested a strong association with the IgG subtype [12]. Irrespective of the subtype, generally it appears that anticardiolipin antibodies may have a direct role in the pathogenesis of haemolytic anaemia in patients with SLE. Other antibodies such as platelet-specific antibodies and antierthrocyte antibodies do also occur [14]. However, antibodies such as anticardiolipin antibodies would best explain the occurrence of both haemolysis and thrombocytopenia in the same patient, rather than limited targets on the respective blood cells. It may be further complicated by the antiphospholipid cofactor specificity, for example β2-glycoprotein I, and the intrinsic heterogeneity for the phospholipid subpopulation [15].

Interestingly, we did not find an association of anti-dsDNA antibodies with either haemolytic anaemia or thrombocytopenia, although Cervera et al. [13] did find an association with haemolytic anaemia (P = 0.003). Using a carefully concentrated cohort analysis we have shown an association of haemolytic anaemia and thrombocytopenia with renal involvement but not renal failure. The outcome of our patients with these severe haematological problems was encouraging in that none of these patients succumbed as a direct result of these complications. Perhaps patients with these autoimmune haematological manifestations have a more benign course of disease? Nossent and Swaak [8] also found no adverse influence on survival in those with haemolytic anaemia and no difference in the incidence of renal or cerebral manifestations. But late-onset thrombocytopenia was associated with decreased survival not attributed to thromboembolic events. However, the numbers in this cohort were small (n = 126).

We also found that a third of patients were not on any treatment at the time of diagnosis. 41% of patients were on prednisolone at <10 mg/day and 41% were on either hydroxychloroquine or azathioprine at the time of the event.

A fifth of patients required splenectomy (we have previously published data on the response to splenectomy in thrombocytopenia [16]; Table 2 in that study demonstrates that this subgroup of patients frequently requires aggressive management, and operative management in the severe group is not infrequent).

Our data demonstrate that both haemolytic anaemia and thrombocytopenia are associated with ACL antibodies and that when faced with a patient with severe haematological manifestations of lupus, active disease in other organs should also be sought.

References


