REVIEW

Anaemia in systemic lupus erythematosus: from pathophysiology to clinical assessment

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Ann Rheum Dis 2006;**65**:144–148. doi: 10.1136/ard.2005.041673

Haematological abnormalities are common in systemic lupus erythematosus. Anaemia is found in about 50% of patients, with anaemia of chronic disease being the most common form. Impaired erythropoietin response and presence of antibodies against erythropoietin may contribute to the pathogenesis of this type of anaemia. Patients with autoimmune haemolytic anaemia usually belong to a distinct category, which is associated with anticardiolipin antibodies, thrombosis, thrombocytopenia, and renal disease, often in the context of secondary antiphospholipid syndrome. Autoantibodies, T lymphocytes, and deregulation of the cytokine network can affect bone marrow erythropoiesis, leading to anaemia.

By incorporating haemocytopenias into the revised American College of Rheumatology criteria for systemic lupus erythematosus (SLE), the experts of the field have acknowledged that the ''haematological system'' is often attacked in this disease. Although lymphopenia is the most common haematological disturbance in SLE, clinicians are often faced with the common problem of a patient with SLE who is anaemic.[1–4]

Although it was initially suspected that anaemia in SLE was mainly a result of antibody induced damage of erythrocytes, evidence to date indicates that the causes of anaemia in SLE vary and that the pathogenesis may be immune or non-immune (table 1).[1 5–7]

Anaemia of chronic disease (ACD), iron deficiency anaemia (IDA), autoimmune haemolytic anaemia (AHA), anaemia of chronic renal insufficiency, and cyclophosphamide-induced myelotoxicity are the most common causes. It is noteworthy that ACD often coexists with anaemia caused by other mechanisms. Iron deficiency is common in patients with SLE as a result of menorrhagia and increased gastrointestinal blood loss, caused by the use of non-steroidal anti-inflammatory drugs, aspirin, and oral anticoagulants.

In this review, we focus on the nature, pathophysiological mechanisms, and causes of anaemia, as well as the clinical approach to anaemia in patients with SLE.

AUTOIMMUNE HAEMOLYTIC ANAEMIA

Antibody-induced damage of blood cells by complement dependent or independent mechanisms has long been considered a common pathogenetic mechanism for cytopenias in SLE. Evidence which restricts bona fide AHA to 5–10% of patients with SLE with anaemia, appears to contradict this hypothesis.[1] The overestimation of the prevalence of AHA in many studies is the result of the inclusion of obscurely defined cases of anaemia, because a positive Coombs' test without actual haemolysis is found in 18–65% patients with SLE.[1]

> ''The prevalence of autoimmune haemolytic anaemia in SLE is often overestimated''

The pathogenesis of AHA should be reviewed within the fundamental immune disturbance of SLE. Interpreting how self intracellular antigens become immunogens effective enough to trigger and maintain a strong and prolonged autoantibody response, is both challenging and crucial. Genetic predispositions and defects in apoptosis, T cell function, and complement or complement receptors are but a few of the numerous abnormalities which have been proposed to underlie lupus pathogenesis, predispose loss of self tolerance, and allow the production of pathogenic autoantibodies.[8–11] In SLE the anti-erythrocyte antibody is mainly warm-type IgG and usually displays non-rhesus specificity.[1] Such antigens are expressed normally by human fetal erythrocytes as early as 10–12 weeks of life. It has been shown in NZB mice, an animal model for SLE, that autoreactive B cells can be sheltered from host erythrocytes entering the peritoneal cavity, an immune privileged compartment that allows them to escape deletion and later produce anti-erythrocyte antibodies, with the appropriate T cell assistance.[12]

The precise specificity of the anti-erythrocyte antibodies for most patients with SLE and AHA is undefined. The non-rhesus-specific IgG autoantibodies in patients with primary AHA have been found to react with either the band 3 anion transporter protein of membrane erythrocytes or with an epitope formed by band 3 protein and glycophorin A.[13] NZB lupus prone mice produce anti-erythrocyte autoantibodies that exhibit anti-band 3 specificity.[14] Interestingly, anti-band 3 IgG antibodies are naturally formed in healthy

Abbreviations: ACD, anaemia of chronic disease; aCL, anticardiolipin antibodies; AHA, autoimmune haemolytic anaemia; APS, antiphospholipid syndrome; BM, bone marrow; EPO, erythropoietin; IDA, iron deficiency anaemia; IFN, interferon; PRCA, pure red cell aplasia; rHuEPO, recombinant human erythropoietin; SLE, systemic lupus erythematosus; TNFα, tumour necrosis factor α

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Accepted 25 July 2005
Published Online First 3 August 2005

Table 1 Causes of anaemia in patients with SLE

Anaemia of chronic disease
Blood loss
Gastrointestinal loss, menorrhagias
Nutritional deficiencies
Iron, folate, B12
Immune mediated
Haemolysis, red cell aplasia, haemophagocytosis, aplastic anaemia, pernicious anaemia
Myelofibrosis
Uraemia
Treatment induced
Microangiopathic haemolysis
Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, drugs
Hypersplenism
Infection
Myelodysplasia

subjects, possibly functioning as eliminators of senescent erythrocytes, which on aging express band 3 protein derived neoantigens.[15] The relation between the naturally occurring and pathological anti-band 3 autoantibodies remains unknown. One might hypothesise that such antigenic neoepitopes, when exposed on senescent red cells, drive autoantibody responses, thereby triggering an autohaemolytic process. This concept stems from considerable data suggesting that the generation and clearance of dead cells are important events that underlie the immunopathology of SLE in general.[11]

Deficient clearance of dead cells is a critical pathogenetic feature of SLE. Macrophages from patients with SLE were proved to be less phagocytic by prolonged half time clearance of Cr labelled anti-IgG sensitised autologous erythrocytes.[16] An interesting, yet unexplained, finding was that patients with SLE and AHA showed an acquired deficiency of either CD55 or CD59 erythrocytic expression, or both, whereas patients with SLE without AHA positively exhibited these molecules.[17] Although the deficiency of these glycoprotein I anchored proteins, whose role is to control complement activity, may contribute to the haemolytic process by increasing the susceptibility to complement mediated lysis, this defect seems to have an enhancing rather than a triggering role. Erythrocytes from patients with paroxysmal nocturnal haemoglobinuria are deficient in a membrane regulatory protein of complement, called decay accelerating factor. Moreover, a functional defect in a second membrane regulatory protein of complement, CR1, has also been proposed; there are also some data about the loss of CR1 on erythrocytes of patients with SLE.[18 19] The loss of glycoprotein I anchored structures might be responsible for some cases of Coombs' negative haemolytic anaemia in these patients.

In patients with SLE, antibodies which react with negatively charged phospholipids such as cardiolipin and putative co-factors have been shown to correlate with venous and arterial thromboses, thrombocytopenia, and recurrent fetal loss—a syndrome called secondary antiphospholipid syndrome (APS).[20] Among patients with SLE, the prevalence of antiphospholipid antibodies is high, ranging from 12% to 30% for anticardiolipin antibodies (aCL), and 15% to 34% for lupus anticoagulant antibodies. Several studies of patients with SLE have shown a significant correlation between aCL or lupus anticoagulant and Coombs' positive haemolytic anaemia.[20–25] Increasing evidence suggests that aCL are not just a secondary phenomenon caused by haemolysis but may also contribute to the pathogenesis of AHA by acting as anti-erythrocyte autoantibodies.[26 27]

It is still unclear whether the presence of AHA worsens the outcome of patients with SLE.[3 28] It has been suggested by one study group that lupus patients with AHA may have a more benign course, but others found differences only in the prevalence of serositis.[29 30] Severe haemolytic anaemia is rather rare and has been significantly associated with other organ disease of, for example, the kidneys and central nervous system.[31] In a retrospective case-control study of our department which assessed the clinical picture, immunological characteristics, and survival of 41 patients with SLE and AHA, two thirds of these patients were found to display autoimmune haemolysis at the onset of SLE.[32] It was further shown that patients with AHA secondary to SLE were more likely to have IgG aCL than controls. The frequency of IgG aCL in this SLE cohort with AHA was 74%, remarkably higher than that previously noted in unselected patients with SLE.[33] In addition, many of these patients had renal disease, thrombocytopenia, and other manifestations of the APS. Thus, autoimmune haemolysis seems to be a marker for a subset of patients with SLE with a higher prevalence of APS.[34 35]

> ''Autoimmune haemolysis seems to be a marker for APS in lupus''

The AHA in patients with SLE is seldom severe and rarely fatal as prednisolone is usually sufficient in controlling it. Should this treatment fail other forms of immunosuppression such as azathioprine and cyclophosphamide as well as danazole, intravenous immunoglobulin, or anti-CD20 monoclonal antibody should be tried. Splenectomy should be considered only as a last resort, given the poor response reported.[36]

SLE: ANOTHER SYNDROME OF IMMUNE MEDIATED HAEMOPOIETIC FAILURE

The concept that haemopoietic failure is the aftermath of an immunologically damaged bone marrow (BM) gathered momentum in the light of evidence produced by the study of BM biopsy specimens from patients with SLE. Overall hypocellularity, morphological dysplasia, increased fibrosis, and BM necrosis were common findings in patients with SLE with haemocytopenias, suggesting a primary BM involvement in the tissue pathogeny of the disease, probably mediated by autoantibodies, immune complexes, and immunopotent T cells.[37 38]

Solid proof of the participation of humoral immune mechanisms in haemopoietic dysfunction was obtained from patients with SLE with aplastic anaemia, a BM failure syndrome of a definite immune pathogenesis. In these rare cases, complement dependent or independent autoantibodies were found to suppress erythroid and granulocytic colony formation of BM progenitor cells.[39–41] In a subsequent study by Liu *et al*, IgG fractions of patients with active SLE and haemocytopenias suppressed BM progenitor growth in vitro, by directly binding CD34+ primitive haemopoietic cells but not more differentiated cells. The nature of the antigen on CD34+ cells still remains an enigma. Furthermore, correlation was not established between the severity of the peripheral cytopenias and the inhibitory capacity of the serum autoantibody on haemopoiesis.[6]

Targeted by autoantibodies, the progenitor BM cells lead to various syndromes of haemopoietic failure, such as aplastic anaemia, hypoplasia of myeloid line, amegakaryocytic thrombocytopenia, and the extremely rare pure red cell aplasia (PRCA).[42–48] The presence of the inhibitory autoantibody is typically related to SLE activity and can be suppressed by successful treatment—that is, by immunosuppression. However, PRCA can occur in the absence of disease activity or even precede the appearance of SLE.[44] In most cases laboratory investigation unmasks the presence of inhibitory

autoantibodies against erythroid progenitor cells, proerythroblasts, and erythropoietin (EPO).[48]

Numerous studies have supported the view that T cell mediated inhibition of haemopoiesis is the major culprit for BM failure in SLE.[45 49–51] Anecdotal reports initially provided laboratory evidence of haemopoietic cell inhibition by reactive T cells, and larger studies employing co-culture experiments and colony formation techniques later confirmed this hypothesis. It has been suggested that the homing of autoreactive lymphocytes in the BM of patients with SLE may affect the haemopoietic capacity of BM stroma and also damage haemopoietic stem cells through direct cytotoxic destruction. Yamasaki *et al* described a series of 25 patients with SLE and anaemia attributed to the suppressor activity of T lymphocytes, which were found to inhibit autologous or allogeneic BM erythroid colony formation in vitro.[50] Removal of T lymphocytes from SLE marrow samples has been reported to significantly increase the progenitor cell clonogenic potential.[42]

> ''T cell mediated inhibition of haemopoiesis is the major cause of bone marrow failure in SLE

That the haematological abnormalities of SLE might not only reflect a process of intramedullary cellular destruction but also, more specifically, apoptosis or programmed cell death, was first proposed by Papadaki *et al*.[52] The authors found that patients with SLE displayed low numbers of CD34+ cells in comparison with controls, which correlated with an increased Fas expression by these cells and high apoptotic indices in the compartment of CD34+/Fas+ cells. In view of these findings, the authors proposed a Fas mediated apoptotic stem cell depletion of SLE marrow, distinctively resembling the apoptotic exhaustion of BM reserve in other syndromes of haemopoietic failure.[53 54]

Fas up regulation on CD34+ cells has been well documented in aplastic anaemia and has been ascribed to increased production of inhibitory cytokines, like tumour necrosis factor α (TNFα) and interferon γ (IFNγ), by BM cytotoxic T lymphocytes. An increased expression of TNFα mRNA has been reported in the BM of patients with SLE, yet the possibility remains that Fas is overinduced in SLE along with several other genes such as CD69 and T cell class II major histocompatibility complex, as part of the broad cellular activation associated with SLE.[55–57] Investigating the root cause of the apoptotic behaviour of SLE haemopoietic progenitors in a more recent study, Tiefenthaler *et al* pointed to the possible involvement of humoral factors.[58] Specific serum samples of patients with SLE with active disease induced apoptosis of allogeneic CD34+ cells, an effect that was found to be independent of complement inhibition and Fas blockade. Unfortunately, the investigators failed to connect the apoptotic process with autoantibody activity because removal of the IgG fraction from the pro-apoptotic sera did not protect CD34+ cells.

Evidence for the culpability of BM stroma in SLE haemopoietic failure derived from culture experiments, in which stromal cells from patients with SLE failed to support allogeneic progenitor cell growth.[52] It has also been shown that as a result of a diminished activity of monocytes the production of haemopoietic growth factors by BM fibroblasts is insufficient, a fact that might explain SLE haematological abnormalities.[59]

PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING ACD IN SLE

Patients with chronic inflammatory disorders, commonly display ACD, a mild to moderate normocytic-hypochromic anaemia the pathogenesis of which remains obscure.[60] Insufficient supply of haemopoietic cells with EPO, together with their resistance to its proliferative action, constitutes an important pathogenetic mechanism of ACD in several autoimmune diseases.[61–63] The phenomenon can be attributed to the impaired EPO resulting from the inhibiting action of inflammatory cytokines such as interleukin 1, TNFα, IFNα, IFNβ, and transforming growth factor β.[64] Experiments have shown that rat kidneys produce less EPO when exposed to interleukin 1.[65] In addition, overproduction of these cytokines has been associated with primary resistance of haemopoietic progenitors to the action of EPO.[66 67]

In a study of our department, assessing whether EPO production is appropriate in patients with SLE with anaemia, haemoglobin levels were correlated with the logarithmic concentrations of EPO measured in patients with SLE with different types of anaemia.[68] A significant increase of EPO was seen with decreasing values of haemoglobin in patients with IDA, but EPO levels, at different values of haemoglobin in patients with ACD and AHA remained unchanged. Moreover, the slope of the EPO response was blunted in ACD and AHA compared with controls, indicating severely impaired EPO production in patients with SLE and ACD or AHA. It has been previously shown that in SLE nephritis, CD4 lymphocytes and macrophages infiltrate the interstitial renal area, producing cytokines inhibiting the production of EPO.[69] Because patients with lupus nephritis often display ACD, inadequate production of EPO in these patients might be due to this mechanism.

The presence of autoantibodies against EPO (anti-EPO) has been proposed as another possible cause of EPO deficiency.[70] Although a correlation between anti-EPO antibodies and EPO levels was not detected in this study, underestimation of EPO measurement due to interference by autoantibodies cannot be excluded in patients with SLE, as proposed by Schett *et al*.[71]

Recent studies have shown that resistance to EPO action can be attributed to autoantibodies against EPO.[72] The possible role of anti-EPO antibodies in the pathophysiology of ACD in patients with SLE was studied by measuring the levels of EPO, as well as the presence of anti-EPO antibodies.[68] Anti-EPO antibodies were detected in 21% of patients with SLE and anaemia, with higher incidence in patients with ACD. These data suggested that patients with anti-EPO antibodies had more active disease, despite the fact that a negative correlation between haemoglobin levels and the presence of anti-EPO antibodies was not proved. However, the presence of anti-EPO antibodies was associated with active SLE and severe anaemia in a previous study.[73] Anti-EPO antibodies were more commonly detected in patients with severe anaemia than in those without. Moreover, patients with SLE with severe anaemia had higher titres of anti-EPO antibodies than patients with SLE with moderate anaemia. The frequent presence of anti-EPO antibodies, particularly in patients with active SLE, ACD, and severe anaemia, implies that anti-EPO antibodies possibly constitute a mechanism of resistance to the action of EPO, justifying the role of anti-EPO antibodies in the pathogenesis of ACD.

CLINICAL CONSIDERATIONS: CONCLUSIONS

Distinctly different therapeutic approaches are required for the multiple causes of anaemia in patients with SLE. ACD is the most common form of anaemia in these patients; AHA, IDA, drug-induced myelotoxicity, and anaemia due to chronic renal failure are also often detected.[1–3 5 68] Aplastic anaemia, PRCA, pernicious anaemia, myelofibrosis, sideroblastic anaemia, haemophagocytic syndrome, and thrombotic microangiopathy occur less frequently.[39 74–80] Given the

complexity of these patients' illnesses, a thorough history and physical examination is essential for placing the anaemia in its proper context.

In clinical practice, simple tests may help to diagnose the underlying cause of anaemia in patients with SLE. For example, if the reticulocyte count is raised, a haemolytic process or acute bleeding should be suspected. Diagnosis of warm-type haemolysis relies on a positive direct Coombs' test combined with reduction of haptoglobin. Increased serum creatinine and blood urea nitrogen levels would indicate poor renal function due to renal disease, which leads to poor secretion and lower serum levels of EPO. Frequently, however, the anaemia in patients with SLE is accompanied by a low reticulocyte count, reflecting a hypoproliferative state. A raised mean cell volume may be an indication of either vitamin B12, folate deficiency or the toxic effects of immunosuppressive agents. A low mean cell volume typically indicates IDA or ACD. Patients with the ACD are characterised by reduced plasma iron and transferrin concentrations, while iron stores, as reflected by plasma ferritin levels, are normal or even increased. The differential diagnosis between IDA and the ACD can now be readily made by measurement of the plasma transferrin receptor concentration and, ideally, determination of the plasma transferrin receptor-ferritin index. BM aspiration can be helpful in evaluating the hypoproliferative anaemia, disclosing deregulation of cellularity, absence of iron stores or megaloblastoid maturation, haemophagocytosis, PRCA, or sideroblastic anaemia.

Based on published clinical trials, recombinant human erythropoietin (rHuEPO) treatment may be beneficial in patients other than those with uraemia. In every day practice, the use of rHuEPO should be limited to patients with symptomatic anaemia and those who are transfusion dependent or candidates for blood transfusion. However, few patients with SLE have haemoglobin levels lower than 80–90 g/l and scarcely any of these patients are transfusion dependent. Thus, although patients with SLE with ACD may show excellent haematological response to rHuEPO, there is little rationale for widespread treatment. Evidence has been provided that rHuEPO treatment is occasionally associated with anti-rHuEPO antibodies which not only inhibit the exogenously administered rHuEPO but also inhibit endogenous EPO, causing PRCA.[81] Moreover, previous studies of the in vitro effects of rHuEPO on T and B cells and studies of lymphocyte subsets in patients undergoing dialysis receiving rHuEPO suggest that rHuEPO might augment immune responses.[82] Should rHuEPO treatment increase autoimmune responses, caution is advised when administering it to patients with SLE.

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