

Haematological manifestations of lupus

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ABSTRACT

Our purpose was to compile information on the haematological manifestations of systemic lupus erythematosus (SLE), namely leucopenia, lymphopenia, thrombocytopenia, autoimmune haemolytic anaemia (AIHA), thrombotic thrombocytopenic purpura (TTP) and myelofibrosis. During our search of the English-language MEDLINE sources, we did not place a date-of-publication constraint. Hence, we have reviewed previous as well as most recent studies with the subject heading SLE in combination with each manifestation. Neutropenia can lead to morbidity and mortality from increased susceptibility to infection. Severe neutropenia can be successfully treated with granulocyte colony-stimulating factor. While related to disease activity, there is no specific therapy for lymphopenia. Severe lymphopenia may require the use of prophylactic therapy to prevent select opportunistic infections. Isolated idiopathic thrombocytopenic purpura maybe the first manifestation of SLE by months or even years. Some manifestations of lupus occur more frequently in association with low platelet count in these patients, for example, neuropsychiatric manifestation, haemolytic anaemia, the antiphospholipid syndrome and renal disease. Thrombocytopenia can be regarded as an important prognostic indicator of survival in patients with SLE. Medical, surgical and biological treatment modalities are reviewed for this manifestation. First-line therapy remains glucocorticoids. Through our review, we conclude glucocorticoids do produce a response in majority of patients initially, but sustained response to therapy is unlikely. Glucocorticoids are used as first-line therapy in patients with SLE with AIHA, but there is no conclusive evidence to guide second-line therapy. Rituximab is promising in refractory and non-responding AIHA. TTP is not recognised as a criteria for classification of SLE, but there is a considerable overlap between the presenting features of TTP and SLE, and a few patients with SLE have concurrent TTP. Myelofibrosis is an uncommon yet well-documented manifestation of SLE. We have compiled the cases that were reported in MEDLINE sources.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease with variable multisystem involvement and heterogeneous clinical features, ranging from mild to life threatening. There is no gold standard

test to diagnose SLE, hence the determination of the presence of this disease, in addition to being a diagnosis of exclusion, ultimately rests with the judgement of a clinician.

The first classification criteria for SLE were developed by the American Rheumatism Association (predecessor of the American College of Rheumatology (ACR)) in 1971.¹ Immunological tests were incorporated into the criteria and revised SLE classification criteria were published in 1982.² The criteria, in 1997, underwent another revision and included advancing knowledge about the association of antiphospholipid (aPL) antibodies with SLE.³ Although the criteria are widely accepted and used, only a few potential manifestations of SLE are represented. The Systemic Lupus International Collaborating Clinics (SLICC) SLE classification criteria comprise 11 clinical and 6 immunological criteria.⁴ In contrast to the ACR criteria, the SLICC criteria require at least one clinical and one immunological criteria for the classification of SLE.²⁻⁴ Autoimmune haemolytic anaemia (AIHA), leucopenia and thrombocytopenia are part of both ACR and SLICC criteria.

Haematological abnormalities are common findings in patients with SLE. Sometimes, haematological abnormalities can be caused by the pathophysiology of SLE itself, but at other times they can be found in patients with SLE but not be a manifestation of SLE. Neither set of criteria, however, specify how leucopenia and lymphopenia in these patients can be differentiated from decreased white cell count caused by immunosuppressive therapy or other causes. Thus, it is important to distinguish haematological abnormalities as either manifestations of SLE, consequence of SLE treatment or as part of another blood cell dyscrasia.

LEUCOPENIA

Introduction

According to the ACR and SLICC criteria for classification of SLE, leucopenia is defined as



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<4000/mm³ on two or more occasions. Along with the pathogenic mechanism of disease itself, several other factors such as immunosuppressive drugs may contribute towards low white cell count in these patients. Leucopenia, that is, low total white blood cell (WBC) count, constitutes a paucity of granulocytes as well as lymphocytes, yet a greater absolute deficiency of granulocytes than lymphocytes is usually found.⁵ Granulocytopenia, or neutropenia, will be the focus of this section, while the next section will discuss lymphopenia, which is the most common WBC abnormality among patients with SLE. Neutropenia is usually defined as an absolute neutrophil count <1000 cells/mm³. Although leucopenia occurs in 50–60% of patients with SLE, only 17% have a WBC count <1000/mm³.^{6–7} The definition of a low total white count or low neutrophil count is complicated by the presence of benign ethnic neutropenia in many (25–50%) persons of sub-Saharan African heritage.⁸ In individuals with this condition, an abnormally low neutrophil count is not easily definable.

Pathogenesis

The pathogenesis of neutropenia in SLE is not entirely understood. Both humoral and cellular immune mechanisms may be involved. Three potential mechanisms of neutropenia in SLE are (1) increased peripheral destruction of granulocytes; (2) changes in marginal and splenic pool, or increased margination; and (3) decreased marrow production.⁹ Yamasaki *et al*¹⁰ studied the pathogenesis of granulopoietic failure in SLE. A decreased number of colony-forming units (CFU) in the bone marrow was demonstrated in 16 women with SLE, and this number was found to correlate with the peripheral granulocyte/monocyte count. This work also found peripheral blood T lymphocytes from three patients with SLE tended to suppress the CFU growth from allogenic normal bone marrow. T lymphocytes from patients with SLE on glucocorticoid therapy did not suppress the CFU growth from allogenic normal bone marrow. According to this study, suppression by T lymphocytes contributed to the decreased marrow CFU, which may play a role in the pathogenesis of granulopoietic failure in SLE.¹⁰

Peripheral destruction of neutrophils is mainly due to circulating antineutrophil antibodies. Starkebaum *et al*⁹ documented neutrophil kinetic studies showing a shortened intravascular survival with an increased marrow neutrophil production. These investigators collected normal control sera from healthy laboratory workers and hospital staff as well as serial serum samples from a patient with SLE over a 2-year course. The IgG neutrophil-binding activity of the patient's serum was elevated in serial samples obtained over the timeframe. Fractions of patient's serum that contained immune complexes failed to opsonise normal neutrophils for ingestion by other normal granulocytes. Enhanced opsonising ability was only displayed by monomeric IgG

fraction of the patient's serum. There were no conclusions drawn on the nature of antigen recognition of neutrophils by the antibodies in this SLE serum. The results of their study, however, suggested an autoimmune mechanism for neutropenia in patients with SLE.⁹

Rustagi *et al*,¹¹ in a study of 18 patients with SLE, suggested complement-activating antineutrophil IgG autoantibodies existed in SLE and their presence correlated with neutropenia. The neutrophil-binding IgG was 2–3 times higher than normal in patients with SLE, yet there was no significant difference in IgG levels between non-neutropenic and neutropenic patients. Complement-induced injury is responsible for some other SLE lesions. So, postulating that neutrophils are affected by complement fixation, with resultant neutrophil depletion, is reasonable. The overall results of this study suggest that the existence of complement-activating antineutrophil IgG autoantibodies correlates with the occurrence of neutropenia. As shown in immune haemolytic anaemia and immune thrombocytopenia, complement fixation by binding of antigranulocyte antibody to the cell surface mediates injury in SLE neutropenia.

Association of anti-Ro (or Sjögren's syndrome-related antigen A (SSA)) antibodies with neutropenia was studied by Kurien *et al*¹² among 72 patients with SLE attending an academic rheumatology clinic. Patients with SLE with anti-Ro autoantibodies were found to have significantly lower neutrophil counts than patients with SLE without anti-Ro. Furthermore, the data indicate that anti-Ro are cross-reactive with a 64 kD protein on neutrophil cell surfaces and may facilitate neutropenia in patients with SLE.¹² If this antigen or another antigen being bound on the neutrophil surface is also present on bone marrow precursors, then there may be a dramatic decrease in peripheral granulocyte levels. Harmon postulated that the mere presence of IgG antibody against peripheral neutrophils may not suffice to cause neutropenia if the bone marrow is able to compensate with healthy production. However, if these antibodies that bind peripheral granulocytes also target marrow precursors, then a more severe neutropenia may ensue by both peripheral destruction and decreased marrow production.¹³

The concept of progenitor cell growth suppression is not new. There is evidence of T cell-mediated or monocyte-mediated suppression of central bone marrow granulocytopoiesis in SLE. Experimental results of Duckham show that whole serum from patients with SLE is associated with bone marrow colony growth retardation in 43% of patients. Whether this suppression is due primarily to colony retardation or colony stimulation factor inactivation is not clear.¹⁴ Yamasaki *et al*¹⁰ studied a population of patients with SLE that exhibited suppression of granulocyte/monocyte colony formation by T cells *in vitro*. This is another mechanism by which neutropenia may be mediated. Fortunately, suppression of granulocytopoiesis rarely results in severe neutropenia.¹⁵

Matsuyama *et al*¹⁶ carried out a study to evaluate the involvement of tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) in the pathogenesis of neutropenia in SLE. This study found serum TRAIL levels to be higher in patients with SLE and neutropenia in comparison to the patients with SLE without neutropenia as well as healthy volunteers. Twenty-eight patients with SLE and eight healthy volunteers participated in the study. None of the patients were on immunomodulatory drugs when blood samples were collected. Duplicate measurement of TRAIL and granulocyte colony-stimulating factor (G-CSF) was carried out by ELISA. Expression of TRAIL receptors on peripheral blood polymorphonuclear leucocytes was obtained by flow cytometry analysis. In total, 15 of 28 patients had neutropenia and serum TRAIL level in patients with SLE with neutropenia was conclusively found to be higher.¹⁶

Clinical presentation

Neutropenia can be one of the contributing factors towards the infectious comorbidity in SLE. Recurrent infections are the only known significant consequence of neutropenia. Local signs and symptoms of infection—ruber, tumour, calor and dolor as originally described by Celsus in the first-century CE—may be attenuated in patients with SLE due to immunosuppression. Constitutional signs and symptoms of infection, such as fever, may also be absent in the immunocompromised patient. Hence, high vigilance is required.

Martinez-Banos *et al* carried out a prospective study that included 126 patients with SLE. Of these patients, 5% had moderate to severe neutropenia (<1000 or <500 neutrophils, respectively).¹⁷ The main aim of their study was to evaluate predisposing factors, clinical outcomes and related prognostic implications of neutropenia in patients with SLE. Among the 33 patients that developed neutropenia, the use of immunosuppressive medication was an independent risk factor for neutropenia as a part of drug toxicity-induced medullary hypoplasia.¹⁷

Sugimoto *et al*¹⁸ encountered a patient with low neutrophil count in the early morning that increased in late morning. This 35-year-old woman, with a 3-year history of SLE, had fever and skin rash on the trunk. Her peripheral neutrophil count was decreased to 280/ μ L, but a blood sample obtained later the very same day showed a neutrophil count of 1400/ μ L. The same pattern was maintained on the third and sixth day of her hospital stay. Her clinical condition, however, improved markedly. Prednisone, 15 mg/day, was being administered at 8:00, and the second blood sample, with the improved count, obtained at 10:00. The authors concluded these diurnal changes were related to the dosing and granulocyte kinetic effects of glucocorticoids on neutrophils.¹⁸

Treatment

As neutropenia in SLE is common and usually mild, there are no current guidelines for therapy and

expectant management is the rule. Treatment is required in severe and life-threatening neutropenia, yet there are no randomised controlled studies to delineate treatment. As with treatment for thrombocytopenia, retrospective case studies may guide current therapy.

Kondo *et al*¹⁹ reported one patient with SLE with agranulocytosis and septic shock who presented with a WBC count of 400/ μ L with no neutrophils. A bone marrow aspirate demonstrated hypocellularity, maturation arrest and an immature myeloid series of 33.8% prior to treatment. A treatment regimen of recombinant human granulocyte (rhG)-CSF and methylprednisolone saw a rapid and sustained resolution of the neutropenia. She was treated with rhG-CSF (100 μ g/day for 5 days) and methylprednisolone pulse therapy (1 g/day for 3 days). Seven days after initiation of treatment, the WBC count was increased to 17 200/ μ L with myeloid series 89.5%. The patient showed significant improvement. Thus, similar to other significant haematological abnormalities in SLE, neutropenia is suppressed by glucocorticoids. But, in this patient, uncertainty exists as to which therapy was responsible for recovery. There may be a synergistic action between methylprednisolone and rhG-CSF.¹⁹

Euler *et al*²⁰ investigated the effect of rhG-CSF on neutrophil count, unaccompanied by immunosuppressive effects of methylprednisolone. In this study, the authors treated three patients with SLE with four cycles of daily subcutaneous filgrastim. In all four treatment cycles, filgrastim resulted in a rapid rise in neutrophil count within 48 h. These investigators concluded that use of rhG-CSF was viable therapy in patients with lupus neutropenia with normal or increased granulopoiesis.²⁰ The authors of the present paper have treated a patient with SLE with persistently severely low granulocyte count (<500/ mm^3 typically) with continuous rhG-CSF for >3 years. A bone marrow examination showed hypercellularity of the myeloid line. She had complete resolution of neutropenic fever episodes, which were occurring several times a year, and she was able to taper glucocorticoid therapy.

Summary

Mild neutropenia is a common finding in SLE that requires no specific therapy. Whether or not this leads to immune suppression is not known. However, a small percentage of patients with SLE develop severe, even life-threatening, neutropenia, which may be caused by a variety of mechanisms, both T cell and B cell mediated. The patient with severe neutropenia with opportunistic infection or the risk of such infection can be successfully treated with G-CSF.

LYMPHOPENIA

Introduction

Lymphopenia is defined as <1.5 \times 10⁹ lymphocytes/L on two or more occasions according to the ACR and SLICC

criteria.^{2–4} Low lymphocyte counts commonly occur in SLE with a prevalence ranging from 20% to 93%²¹ and are observed frequently in patients with active or severe disease.²² Moreover, lymphocyte levels may fluctuate during the clinical course, irrespective of treatment.²¹ However, glucocorticoids and immunosuppressive drugs may contribute to the lymphopenia in severe disease. The degree of lymphopenia can be quite striking with values $<0.5 \times 10^9/L$ observed in 10% of patients. Lymphopenia occurs independently of neutropenia but may also contribute to the leucopenia seen in these patients.

Both T and B lymphocyte subpopulations may be affected, whereas the null lymphocyte subpopulation is frequently spared.²³ T cell numbers are affected more than B cells.²² In particular, the CD4+ subset of T cells is more profoundly affected, although the CD4/CD8 ratio is usually unchanged.²⁴ This surprising observation may be explained by the deficiency of the CD4 epitope that reacts with monoclonal antibody used for the detection of this subset, leading to a technical artefact.²⁵ The naive B lymphocyte subset (CD19+/CD27–) is more affected than the memory B lymphocyte subset (CD19+/CD27+) in patients with active SLE.²⁶

Pathogenesis

The pathogenesis of lymphopenia is still unclear. Antilymphocyte antibodies have long been held responsible for the decline in lymphocyte numbers and in lymphocyte function. The number of autoantibody types responsible for these activities has expanded in the last several decades.²⁷ Recent studies suggest that defects in apoptosis may also play a role.^{28–29}

Antilymphocyte antibodies are a heterogeneous group of autoantibodies. Titres vary with disease activity, and presence of antilymphocyte activity is associated with lymphopenia. Historically, these antibodies have been identified *in vitro* by their ability to lyse lymphocytes. More recently, these antibodies have been identified by their binding to the surface of lymphocytes or plasma membrane components. Other autoantibodies, for example, anti-Ro, are associated with lymphopenia.³⁰

Circulating lymphotoxic antibodies are commonly identified in SLE, and levels correlate with lymphopenia.³¹ Such antibodies are identified by their ability to mediate complement-mediated lymphocyte toxicity at 15°C. The prototypic antibodies are cold-reactive IgM antibodies. Some targets have been defined and include CD45 and peptides of the T cell receptor, among others. IgG antilymphocyte antibody has also been described. These antibodies have the potential to deplete lymphocytes by antibody-dependent cellular toxicity. Their molecular targets include but are not limited to human leucocyte antigen class II antigens, interleukin (IL)-2 receptors, soluble products of activated T cells, glycosphospholipids³² and the ribosomal P protein.³³

Lymphocyte apoptosis may also contribute to lymphopenia in patients with SLE. Accelerated *in vitro*

apoptosis of lymphocytes and increased amounts of circulating apoptotic bodies have been demonstrated.³⁴ Upregulation of fas antigen on naive peripheral T cells may contribute to increased apoptosis.³⁵ In contrast, this subpopulation of T cells is relatively devoid of fas antigen in normal individuals and those with rheumatoid arthritis. These T cells may be highly susceptible to fas-mediated apoptotic cell death. Silva *et al* also observed increased apoptosis in SLE lymphocytes compared with healthy controls. Neglect apoptosis, which is independent of fas–fas ligand binding and occurs with the loss of survival stimuli, was responsible for this finding.²⁹ Lymphocytes from patients with neuropsychiatric lupus were particularly susceptible to this form of apoptosis, especially in the presence of autologous sera containing aPL or anti-Ro antibodies.²⁹

The past decade has put forward more studies correlating leucopenia with specific antibodies targeting nuclear antigens. Blood samples of 82 patients seen between 1998 and 2001 were included in a study by Wenzel *et al*. Leucocyte subsets were measured using flow cytometry, with autoantibodies detected by indirect immunofluorescence and ELISA. A number of peripheral leucocyte subsets were lower in autoantibody-positive patients in comparison with patients without these antibodies.³⁶ Hence, this study showed a possible interaction between these antibodies and lymphocyte subpopulation *in vivo*.³⁶

Clinical presentation

Presence of lymphopenia may be clinically silent or associated with increased risk of infections and/or active SLE. Data on the increased risk of infection are controversial and are complicated by the use of immunosuppressive therapies. Ethnicity may also play a role in explaining the conflicting results.

Life-table analysis of patients in the Netherlands from 1991 showed no effect of lymphopenia on patient survival.³⁷ In contrast, marked T cell depletion was associated with serious and often multiple infections in severely affected patients with SLE in India.²² However, high-dose glucocorticoids and cyclophosphamide use make these latter results difficult to interpret. One study found the combination of severe lymphopenia, values $<0.35 \times 10^9/L$, and immunosuppressive therapy increases risk of *Pneumocystis jirovecii* pneumonia.³⁸ Nonetheless, Ginzler's summary of the literature supports the premise that SLE is associated with increased infections even in the absence of immunosuppressive drugs.³⁹ Most studies have generally found that increased disease activity associates with increased risk of infections. Uraemia and immunological dysfunction are considered the major risk factors for infection. Lymphopenia, especially affecting T cells, likely contributes to this dysfunction.

Some authors, but not all,⁴⁰ have shown that lymphopenia correlates with disease activity. Fever, polyarthritis, as well as central and peripheral nervous system disease, in particular, are associated with lymphopenia.

Development of lymphopenia during the course of disease is frequently associated with disease relapse.²¹ Mirzayan *et al*, in their prospective study to characterise prognostic parameters for SLE disease flares, concluded lymphopenia to be one of the predictors of flares. The authors evaluated 120 patients every three months for 2 years. At every visit, clinical manifestation and laboratory parameters were assessed and systemic lupus erythematosus disease activity index (SLEDAI) was determined. All patients were in clinical remission at enrolment. The authors conclusively stated that flares in SLE could be predicted by lymphopenia.⁴¹ Lymphocyte counts also frequently rose with disease remission.²¹ Therefore, lymphopenia may have prognostic significance.

Treatment

There are no recommendations for treatment specifically for lymphopenia analogous to those for haemolytic anaemia or thrombocytopenia. However, treatment for other clinical aspects of disease activity can lead to improvement in lymphocyte counts.²¹ Use of prophylaxis against *P. jirovecii* should be considered in patients with lymphocyte counts $\leq 0.35 \times 10^9/L$.³⁰ Belimumab, a monoclonal antibody that impairs B lymphocyte survival by binding B lymphocyte stimulator (BLyS), is efficacious as add-on therapy in patients with SLE with uncontrolled disease activity. A recent analysis of the effect of this drug on organ-specific disease activity has been reported in which data from the two randomised, placebo-controlled trials were pooled.⁴² This study shows no improvement of lymphopenia at either dose of belimumab among patients with baseline haematological involvement (n=137).

Summary

Lymphopenia may occur by interplay of different mechanisms. Specific therapy for lymphopenia is not indicated in patients with SLE, but lymphopenia, and its degree, may be related to the disease activity. Severely low lymphocyte count may predispose patients to opportunistic infections such that prophylactic therapy should be considered, especially in those patients on immunosuppressive therapy.

THROMBOCYTOPENIA

Introduction

For the purpose of the ACR classification criteria for SLE² and the new SLICC criteria,⁴ the definition of thrombocytopenia is a platelet count $< 100\,000/mm^3$ (or $100 \times 10^9/L$) without any other identifiable cause. Excluding thrombocytopenia as a result of pharmacological therapy may be especially difficult in patients with SLE. Pseudothrombocytopenia must be excluded by careful examination of the peripheral blood smear in order to determine whether platelet aggregation along with adherence to leucocytes has occurred.

Pathogenesis

True thrombocytopenia can occur by three mechanisms: impaired production of platelets in the bone marrow, sequestration of platelets in the spleen or accelerated destruction of platelets in the peripheral circulation. The majority of patients with SLE with thrombocytopenia have increased peripheral destruction that is commonly mediated by antiplatelet antibodies, but the other two mechanisms play a role in some patients.⁴³

Autoantibodies

Antiplatelet antibodies and their antigenic targets have been extensively studied in both isolated idiopathic thrombocytopenic purpura (ITP) and SLE.^{43–45} Clear immunological differences between antiplatelet antibodies are found in the two illnesses. In addition, differences in the autoimmunity directed against platelets among subsets of patients with SLE, especially when stratified according to the presence of aPL antibodies, are described.⁴⁵

Similar to isolated ITP, both serum platelet-binding IgG and platelet-associated IgG are increased in patients with SLE with thrombocytopenia^{44 46}; however, these antibodies are also commonly present in the serum of patients with SLE without thrombocytopenia.⁴⁷ In a group of 90 patients with SLE, of whom 29 had thrombocytopenia, there was no statistically significant correlation between the presence of antiplatelet antibodies and different disease manifestations except for thrombocytopenia.⁴⁸ Nonetheless, in 25 patients without a history of thrombocytopenia, antiplatelet antibodies were associated with active disease.⁴⁸

As mentioned before, the targets of the immune response against platelets in patients with SLE differ from the targets seen in patients with isolated ITP. In ITP, patient antibodies bind platelet surface glycoproteins such as GP IIb/IIIa, Ib/IX and Ia/IIa.⁴⁹ Meanwhile in patients with SLE, one study found almost no binding of platelet glycoproteins.⁵⁰ Instead, immunoblot studies of platelet eluate showed binding of a species migrating at 50–70 kD, the binding of which was inhibited by lysed platelets.⁵⁰ Another study found binding to a similarly migrating species as well as one migrating at 80 kD.⁵¹ The specificity of aPL may vary according to the association with thrombocytopenia. In particular, antiprothrombin antibodies are commonly found in patients with aPL and thrombocytopenia.^{52 53} Whereas the proposed mechanism of thrombocytopenia in ITP is loss of immunological tolerance to specific platelet-associated antigens, thrombocytopenia in SLE may be caused in some instances by a more complex interaction between aPL antibodies and platelet-antigen antibodies.

As discussed above, thrombocytopenia in the setting of lupus is associated with aPL antibodies. A prospective, cohort study of 390 patients with SLE found that of 18 patients with thrombocytopenia 14 had anticardiolipin (aCL) antibodies, one of the many antiphospholipid

antibodies. In total, 47% of the entire group had these antibodies. Thus, the relative risk for thrombocytopenia in patients with aCL antibodies was greater than four.⁵⁴ Another study assessed the fine specificity of antiphospholipid antibodies and found that aCL, antiphosphatidic, antiphosphoserine, antiphosphoinositol as well as the lupus anticoagulant were all associated with thrombocytopenia.⁵⁵ In a series of 125 consecutive women with a lupus anticoagulant, 30 met criteria for SLE and 8 of these 30 patients had thrombocytopenia as a manifestation of SLE. Thus, there is a significant connection between the presence of the lupus anticoagulant and thrombocytopenia in patients with SLE.⁵⁶ The known association of thrombocytopenia with the presence of aPL antibodies may,^{53–59} at least in some patients, be related to a common or a cross-reactive antigen since binding of some aCL antibodies can be inhibited by washed platelets.⁵⁹

Genetics

Genetic studies in SLE have been largely at the level of disease thus far, but a few have examined the genetics of severe disease and/or disease manifestations. We found⁵⁷ and confirmed⁶⁰ genetic linkage among American black families in which SLE is manifested by thrombocytopenia on chromosome 11p13.⁶⁰ Of course, this ethnic group is well known to have not only an increased risk of SLE but also a more serious disease than any other ethnic groups studied so far. Fine genetic mapping of this genomic region using single-nucleotide polymorphisms shows genetic association near the CD44 gene.⁶¹ Unfortunately, a putative disease-causing allele has not been identified as yet. Other data also suggest that thrombocytopenia in SLE might have a genetic component as this manifestation is likely to be shared by SLE-affected siblings.⁶²

Subsequent to the previously cited genetic linkage work, a number of other studies have found the genetics of SLE to be related to thrombocytopenia (table 1). In most of these studies, the genetic effect was enhanced by comparing SLE with or without thrombocytopenia, or by limiting the analysis to patients with thrombocytopenia. However, in a few studies, the genetic allele under investigation showed a statistical relationship to the presence of thrombocytopenia, not to the disease itself.⁶³ Whether these findings represent genetics directly related to the mechanism of low platelets or to thrombocytopenia as a marker of severe disease remains to be determined. Most of these studies parsed SLE by many manifestations with a few studies making statistical correction for multiple comparisons. We conclude that if such corrections were made then many of the findings (see table 1) would lose statistical significance.

Other

Macrophage activation syndrome is another cause of thrombocytopenia in connective tissue diseases, including SLE.⁶¹ Early suspicion with cytopenias including low

platelet counts, dropping erythrocyte sedimentation rate, high ferritin and elevated triglycerides hold the key to successful treatment of this potentially fatal entity. Treatment usually consists of high-dose glucocorticoid along with other cytotoxic agents.

Clinical presentation

Thrombocytopenia in SLE can present in multiple ways. Isolated ITP may be the first manifestation of SLE and precede other aspects of SLE by months or even years. Some individuals, 12% in one series of 115 patients with ITP, go on to develop SLE⁶⁴; therefore, some patients with SLE have isolated ITP prior to developing classifiable SLE. However, the number of patients with SLE who present initially with ITP is not precisely known.

Thrombocytopenia in patients with established SLE can be thought of broadly in two categories, although these are not exclusive.⁶⁵ One group of patients has thrombocytopenia as part of a generalised exacerbation of SLE. These patients can have very low platelet counts with danger of life-threatening haemorrhage. The platelet count in these patients usually responds acutely to treatment with glucocorticoids. Approximately the other half of patients with SLE with thrombocytopenia has a more chronic form that is at times present even when other aspects of the disease are quiescent. These patients may not respond as well to glucocorticoid therapy. However, they are also more likely to have only a modest decrease in the platelet count that may not require specific therapy. Overall, 10–15% of patients with SLE have thrombocytopenia as a manifestation of their disease.

In addition to life-threatening haemorrhage as a direct result of low platelets, other serious SLE manifestations occur more frequently among patients with SLE with thrombocytopenia. These correlates of low platelet count include neuropsychiatric manifestations,⁶⁶ haemolytic anaemia,^{65 67} antiphospholipid syndrome⁴⁵ and renal disease.^{65 68} Our group studied thrombocytopenia in a large cohort of 179 families in which each family had at least two members with SLE.⁵⁷ Thrombocytopenia was strongly associated with several manifestations of SLE including haemolytic anaemia, neuropsychiatric disease and renal disease. Almost half of the patients with either thrombocytopenia or haemolytic anaemia also had the other manifestation. In addition, thrombocytopenia was associated with aPL, antiribonucleoprotein and anti-Ro (the last in African-American patients only). Results show that SLE is more severe in the families with a patient with thrombocytopenic SLE.⁵⁷

In addition to the association with more severe disease, data show an association between thrombocytopenia and outcome. Although patients with SLE rarely die of bleeding complications, those patients with thrombocytopenia have a poorer prognosis.^{45 54 68–72} Two studies of SLE, both large and long term, have shown that thrombocytopenia was the only, or nearly the

Table 1 Genetics of systemic lupus erythematosus (SLE) for which thrombocytopenia was found to define or enhance the effect

Author	No. of patients	Ethnicity	Gene (SNP)	Technique	Effect size
Scotfield ⁵⁷	184 families*	North Am	11p13 near CD44	Genetic linkage	LOD score=3.71 in all LOD score=5.71 in AA
Trivedi ¹⁵⁴	252	North Am	Osteopontin/rs11730582C	Candidate gene/SNP typing genetic association	OR=2.1
Piotrowski ⁶³	199	Poland	Monocyte chemoattractant protein 1/rs1024611	Candidate gene/SNP typing genetic association	OR=2.62
Amengual ¹⁵⁵	134	Japan	Human platelet antigen 6	Candidate gene/RFLP genetic association	OR=8.0
Nolsoe ¹⁵⁶	126 families*	North Am	FAS and FAS ligand Codon214AC	Candidate gene/SNP typing transmission disequilibrium	p=0.006
Namjou ¹⁵⁷	7490	North Am	TRAF6/rs5030470	Candidate gene/SNP typing genetic association	OR=0.57
Jeon ¹⁵⁸	147	Korea	IL-6 3'/IL-6 33	Candidate gene/VNTR K9 logistic regression inheritance models	p=0.02
Jeon ¹⁵⁹	147	Korea	IL-6/-278AC	Candidate gene/SNP typing genetic association	p=0.006
Chan ¹⁶⁰	107	Taiwan	Suppressor of cytokine signalling 1/-1478CA/del	Candidate gene/SNP typing dominant inheritance model	p=0.007
Kim ¹⁶¹	148	Korea	C reactive protein/-390CA	Candidate gene/SNP typing genetic association	p=0.043
Warchol ¹⁶²	102	Poland	Catalase/-330CT	Candidate gene/RFLP typing recessive inheritance model for CC genotype	OR=7.4 p=0.0017
Hong ¹⁶³	183	Korea	FcgammaRIIIB/NA1/NA2	Candidate gene/SNP typing genetic association	OR=2.4 p=0.04

*Families in these studies all had at least two patients with SLE.

AA, African-American; IL, interleukin; LOD, logarithm of odds; RFLP, restriction fragment length polymorphism; SNP, single-nucleotide polymorphism.

only, independent risk factor for early mortality in SLE. These studies involved European-American, Hispanic and African-American patients with SLE.^{70 71} Other studies involving different ethnic groups and other parts of the world (Chile, Canada and Southern China) also demonstrate poorer survival in patients with SLE with thrombocytopenia. While a few studies show no influence of thrombocytopenia on survival,^{64 73} most do show an effect with the relative risk for death during the period of follow-up being increased from 1.5-fold to 45-fold.^{45 54 68–70} Thus, based on outcome studies and cross-sectional studies of disease associations, thrombocytopenia can be regarded as an important prognostic indicator for SLE patient survival.

Medical treatment

Thrombocytopenia in patients with SLE presents a wide range of clinical scenarios ranging from mild and asymptomatic, requiring observation only, to severe and immediately life-threatening, requiring aggressive immunological and/or surgical therapy. No randomised controlled clinical trials are available to guide therapy, and future such trials evaluating different therapies for thrombocytopenia in SLE are unlikely. With a few notable exceptions, retrospective case series are the most prevalent types of studies

published. These studies have inherent problems such as non-randomisation that can bias conclusions. Fortunately, most patients with SLE with thrombocytopenia need only expectant observation, not specific treatment. With a platelet count $>40\,000/\text{mm}^3$, no specific treatment for the thrombocytopenia is required unless there is excessive bleeding. In fact, most patients do not need therapy as long as the platelet count exceeds $20\,000/\text{mm}^3$.

On the other hand, in patients with very low platelet counts or modestly low platelet counts along with bleeding, glucocorticoid is the first-line therapy. Arnal *et al*⁷⁴ studied 59 patients with SLE with thrombocytopenia, who were treated at five French centres. Of these 59 patients, 57 received oral glucocorticoid as first and sole therapy; and of these, 50 were evaluated long term (the remaining 9 received some other therapy in addition to glucocorticoid and were excluded from the evaluation). Of these 50, 40 had an acute response to glucocorticoid therapy that resulted in a rise in the platelet count. However, only 11 had a sustained response in mean follow-up of 78 months. Also, 8 of these 11 patients had normal platelet counts and were free from therapy after an average of 13 months of glucocorticoid therapy. Thus, the sustained remission rate was low (22%), and ultimately, 78% of the patients were classified as long-

term failures. In this same study, 10 patients were treated with high-dose intravenous methylprednisolone with an initial response rate of 60%; however, no patient had a sustained response,⁷⁴ although one patient with a sustained response has been reported.⁷⁵ Thus, oral or high-dose intravenous glucocorticoids produce a response in the majority of patients initially, but sustained response to this therapy is unlikely. Nonetheless, this therapy may be extremely useful in the patient with severe thrombocytopenia.

Danazol, a weak androgenic steroid, has also been used in the treatment of thrombocytopenia caused by SLE, although its complete mechanism of action is still unknown (table 2).^{74 76–79} Several case reports demonstrate success in patients that have failed other treatments.⁷⁶ In a randomised controlled blinded trial of danazol in seven patients with mild SLE, the main effect noted was improvement of thrombocytopenia. With 1 month of danazol therapy, preceded and followed by 1 month of placebo, the three patients with thrombocytopenia all had improvement of the platelet count.⁷⁷ In another study, West and colleagues used danazol (800 mg/day initially for 8 weeks) in six patients with SLE with severe thrombocytopenia, all of whom had failed glucocorticoid treatment. Four of the six had failed splenectomy.⁷⁹ At 8 weeks, all had normal platelet counts and were on lower doses of glucocorticoid. Five were followed for 1 year, and all maintained a normal platelet count on lower doses of danazol, ranging from 200 to 600 mg/day. However, there was no evidence in this study of a reduction of platelet-bound immunoglobulin or circulating immune complexes.⁷⁹ In 1997, four patients with SLE were reported with thrombocytopenia refractory to prednisone in whom danazol restored a normal platelet count. A sustained response was noted in follow-up of 18–36 months.⁷⁸ The Arnal study had 18 of 59 French patients on danazol in addition to prednisone. Danazol was added in 12 of the 18 patients because they had failed another treatment.⁷⁴ A sustained response was noted in nine with mean follow-up of 28 months.⁷⁴ Another relatively large study of danazol followed 16 consecutive patients with SLE with thrombocytopenia from a single centre over a 5-year period. All had a good or excellent response within two months to danazol, which was started at 200 mg/day and increased by 200 mg every four weeks until a response was noted. All patients had failed oral glucocorticoid and five had not responded to splenectomy. In an average follow-up of 18.2 months (range from 2 to 49 months), danazol was tapered to between 200 and 400 mg/day without a recurrence of thrombocytopenia.⁸⁰ Thus, the data indicate that danazol is an effective therapy for thrombocytopenia in SLE, even after failure of glucocorticoid.

Another medical therapy is hydroxychloroquine. Arnal *et al*⁷⁴ treated 11 of 59 patients with hydroxychloroquine, which was added to oral glucocorticoid in all patients. Of these 11 patients, 7 had a sustained

response in mean follow-up of 31 months, with prednisone dose <0.2 mg/kg/day in all 7 patients. There is no other report of hydroxychloroquine therapy in SLE thrombocytopenia to our knowledge. One patient has been reported to respond favourably to dapsone, which was begun for the treatment of cutaneous involvement of SLE.⁸¹

Another useful therapy is intravenous immunoglobulin (IVIG), although the effectiveness is also short term. Maier *et al*⁸² studied seven patients with SLE who received IVIG 400 mg/kg for five consecutive days and then monthly for 1 year. Four had a favourable response at 5 days, but the platelet count was maintained in only two at 28 days, with only one patient having a sustained response at 1 year.⁸² Another report also demonstrates the short-term efficacy of IVIG but no long-term response.⁸³ Meanwhile, other reports have demonstrated the efficacy of this treatment in the acutely bleeding thrombocytopenic patient with SLE.^{84 85}

Other immunosuppressants have been studied in SLE-related thrombocytopenia. In an early study by Ahn and colleagues, vincristine was used in 10 patients, 3 of which had convincing SLE by application of present criteria.^{2 4} Two of the three patients responded positively to vincristine, although the duration of the responses was not reported.⁸⁶ Nevertheless, therapy with vincristine can be limited by the side effects, which include neuropathy and bone pain. Cyclosporin, in low doses, has also been successfully employed,⁸⁷ including in three patients who were not responsive to multiple therapies and in whom clinically important bleeding was occurring.⁸⁸ In addition, cyclosporin improved platelet counts in 3 out of 3 thrombocytopenic patients among 16 who were receiving the drug for SLE therapy.⁸⁹ The cytotoxic agent cyclophosphamide had a positive effect in a patient with SLE who had recurrent thrombocytopenia 7 years after splenectomy but who failed intravenous glucocorticoids and a short course of danazol.⁹⁰ Boumpas *et al*⁹¹ treated seven patients with thrombocytopenic SLE with cyclophosphamide and found platelet count recovery in all between 2 and 18 weeks. Six of these seven patients received the drug for renal disease and one for thrombocytopenia alone. In follow-up ranging from 12 to 74 months, all patients maintained a normal platelet count only on low-dose prednisone, but two patients required maintenance doses of cyclophosphamide.⁹¹ There are case reports of the successful treatment of thrombocytopenia with mycophenolate mofetil.^{92–94}

The experience of Arnal *et al*⁷⁴ was not nearly as positive with regard to immunosuppressant therapy for thrombocytopenia. Of their 59 patients with SLE-associated thrombocytopenia, 14 received immunosuppressant-containing regimens, which included azathioprine, cyclosporine, cyclophosphamide, vincristine or vinblastine added to prednisone, splenectomy, IVIG, danazol or hydroxychloroquine. Only 2 of the 14 patients receiving immunosuppressants had a sustained platelet response, and both were on vinblastine. In fact, better responses

Table 2 Use of danazol in systemic lupus erythematosus (SLE) thrombocytopenia

Author	No.	Design	Remission (%)	Dose	Duration	Comment
Marino ⁷⁶	3	Series	3 (100%)	200–600	Prolonged	Failed intravenous Ig, intravenous glucocorticoids and splenectomy
Agnello ⁷⁷	3	RBPCT	3 (100%)	600	1 month	Mild SLE, 7 patients in trial, 3 with low platelets
West ⁷⁹	6	Series	6 (100%)	800	1 year	All failed glucocorticoids, 4/6 failed splenectomy
Blanco ⁷⁸	4	Series	4 (100%)	400–800	18–36 months	All failed glucocorticoids and at least one other drug
Cervera ⁸⁰	16	Series†	16 (100%)	200‡	2–49 months	All failed glucocorticoids, 5 failed splenectomy
Arnal ⁷⁴	18	Series	9 (50%)	400–600	28 months	All treated with glucocorticoids

Dose is given as milligram per day.

†This was a consecutive series of patients with SLE with thrombocytopenia and bleeding.

‡200 mg/day initially, then increasing 200 mg each week until a response was noted.

RBPCT, randomised blinded placebo-controlled trial.

were found in the patients on non-immunosuppressive therapy, but those 14 patients given immunosuppressive therapy may have been sicker.

Biological treatment

The newer biological therapies may be an important alternative in patients with SLE with thrombocytopenia. There are data in regard to use of B cell-depleting therapy with rituximab in patients with SLE with thrombocytopenia.⁹⁵ Lateef *et al*⁹⁶ used this drug in the treatment of 10 patients with refractory disease, of whom 3 had thrombocytopenia. The indication for rituximab was persistent, severe thrombocytopenia in two of these three. All three had undergone several unsuccessful therapies prior to rituximab treatment, including cyclophosphamide, mycophenolate, cyclosporine, hydroxychloroquine and glucocorticoid. The platelet count rose in all three patients, and in two of the three the rise was sustained and to $>100 \times 10^9/L$ ($100\,000/mm^3$). Another report was in 52 Hispanic patients with SLE, all with refractory disease and treated with rituximab.⁹⁷ Eight of these patients had thrombocytopenia. Similar to the previously discussed report, platelet count rose significantly in all from an average of $69 \times 10^9/L$ ($69\,000/mm^3$) to $182 \times 10^9/L$ ($182\,000/mm^3$) at 6 months. Oral prednisone dose was reduced from about 28 mg/day on average to 11 mg/day in these patients. There has been a study of low-dose rituximab (100 mg/week for 4 weeks) in 10 lupus patients with thrombocytopenia. The time to complete remission may have been slower in these patients and less durable. Two patients relapsed at 36 weeks.⁹⁸ Thus, anti-CD20 therapy with rituximab has been used in a small number of patients with SLE with thrombocytopenia and is effective, although there are reports of thrombocytopenia refractory to rituximab.⁹⁹

High success rate with rituximab in children with thrombocytopenia, including those with SLE, has also been documented in a systematic review.¹⁰⁰ Kumar and colleagues at the Hospital for Sick Children (Toronto, Ontario, Canada) carried out a retrospective cohort study. The aim was to determine long-term safety and efficacy of B cell depletion therapy for children with autoimmune thrombocytopenia and AIHA in paediatric

SLE.¹⁰¹ Nine patients with paediatric SLE were included in the study. Five had autoimmune thrombocytopenia, three had AIHA and one had both. Two of these had a relapse at 48 and 64 weeks from the treatment. Both of these received a second course of rituximab with platelet count rising to $>100 \times 10^9/L$ ($100\,000/mm^3$). Two of the five had glucocorticoid therapy stopped while the other three continued on intermittent glucocorticoid.

IL-11 is a thrombopoietic factor produced by bone marrow stromal cells, and recombinant human IL-11 is approved for use in the USA for the treatment of cancer chemotherapy-induced thrombocytopenia. In one report, this drug was used in a 38-year-old patient with SLE with life-threatening thrombocytopenia associated with intrabronchial bleeding. The platelet count had not responded to IVIG, high-dose methylprednisolone, cyclophosphamide or plasma exchange, but did respond to IL-11 over a 5-day period with platelets rising to $50\,000/mm^3$ and control of bleeding.¹⁰²

Surgical treatment

Splenectomy has been used in patients with SLE with thrombocytopenia with success; however, many of the earlier studies on this procedure failed to define or report follow-up of the patients.^{103–105} Coon reported 18 patients with SLE in whom the principal reason for splenectomy was thrombocytopenia, in which only one patient was said to have periodic relapses requiring glucocorticoid. Unfortunately, neither the individual nor the mean length of follow-up is given, although eight patients were followed <1 year.¹⁰³ Similarly, in another study of splenectomy for patients with glucocorticoid-resistant thrombocytopenia in SLE, of 12 patients 8 had excellent outcomes.¹⁰⁴ Another report of six patients with SLE with thrombocytopenic shows five off therapy, but again the length of follow-up is not well defined.¹⁰⁵ One other uncontrolled, but more well described, study of splenectomy in SLE-induced thrombocytopenia has had much less favourable results.¹⁰⁶ Among 14 patients with SLE undergoing splenectomy over a 22-year period, 5 had persistently low platelets, 3 recurred within 6 months, 3 recurred >6 months after their surgery and only 2 had a normal platelet count without glucocorticoid therapy.¹⁰⁶

Among the 59 patients followed by Arnal *et al*,⁷⁴ 17 underwent splenectomy with a sustained response in 65%, in follow-up ranging from 3 to 209 months (mean 65 months). One patient among those undergoing a splenectomy died of *Staphylococcus aureus* sepsis while no patient with an intact spleen did so. Thus, uncontrolled studies of splenectomy have given mixed results with recurrence of thrombocytopenia relatively common.

One group has attempted a controlled, matched study of splenectomy in SLE.¹⁰⁷ Fifteen patients with SLE undergoing splenectomy for haemocytopenias were compared with 15 matched patients with SLE with haemocytopenias who had not undergone splenectomy. The patients were highly similar in all clinical aspects prior to splenectomy. Clinical course after splenectomy was compared with an equivalent period in the matched patients. In the splenectomised group, there was a higher incidence of death (4 vs 1), cutaneous vasculitis, higher-dose prednisone requirements, more immunosuppression (10 vs 3) and more infection (18 vs 2). Two of the splenectomy patients died of infection. Remarkably, the degree and number of haemocytopenias were similar between the two groups after splenectomy compared with the control period in the patients not undergoing a splenectomy. In contrast, a different study followed nine patients with SLE undergoing splenectomy for thrombocytopenia and reported no worsening lupus or infection in mean follow-up of 93 months.¹⁰⁸

Summary

Many patients with thrombocytopenia as a manifestation of SLE can be watched without specific treatment directed at the low platelet count, and the great majority of those requiring treatment can be successfully managed. For acute treatment, glucocorticoid is the mainstay of therapy, but a sustained response is unlikely. Either danazol or hydroxychloroquine can be added to glucocorticoid therapy, followed by slow taper of the glucocorticoid. If these therapies are not effective, then a trial of immunosuppressive therapy may be warranted in the form of cyclophosphamide. Very low dose cyclosporin or vincristine can also be considered. There are emerging data that rituximab is an effective therapy in patients with refractory thrombocytopenia. As emphasised by an editorial,¹⁰⁹ splenectomy results in a 50–66% remission rate, but the only controlled trial in regard to splenectomy as a therapy for thrombocytopenia in SLE indicates a very high rate of subsequent infection, which may be life threatening. Thus, splenectomy should be reserved as a last resort in patients with SLE. For emergent treatment of thrombocytopenia in the patient with SLE, several therapies will likely be given simultaneously. Both high-dose glucocorticoid and IVIG have been shown to be effective in this situation and can be used together. One report found IL-11 useful, and this drug should be considered in a patient not responding adequately to the first two choices. Finally, plasma exchange is of proven benefit in thrombotic thrombocytopenic

purpura (TTP) and has been effective in several patients with SLE with serious, glucocorticoid-refractory thrombocytopenia and bleeding.^{110 111} Use of aphaeresis should be considered in a patient with thrombocytopenia and life-threatening bleeding not responsive to other therapies.

AUTOIMMUNE HAEMOLYTIC ANAEMIA

Introduction

The ACR and SLICC criteria recognise AIHA with reticulocytosis as one of the criteria for the classification of SLE, while the SLICC criteria also include a positive Coombs test as a criterion.

Pathogenesis

Antierthrocyte antibodies in SLE are mainly warm-type IgG. aPL antibodies associate with Coombs-positive haemolytic anaemia in patients with SLE.¹¹² aCL antibodies, IgG and IgM, are more common in patients with SLE with AIHA.¹¹³ Lang *et al*,¹¹⁴ in their comparative study, provided evidence delineating the role of aCL antibody in AIHA.

The lupus-prone mice, New Zealand black, produce antibody 3-specific antibodies.¹¹⁵ Antiband 3 IgG antibodies are also possibly involved in removal of aging red blood cells from the circulation of healthy individuals.¹¹⁶ As in primary AIHA, warm-type IgG react with band 3 anion transport protein. Regardless of this knowledge, an association between AIHA in patients with SLE and antigen specificity has not been determined. Underexpression of CD55 and CD59 has been shown on erythrocytes of patients with SLE-associated AIHA.¹¹⁷ These membrane proteins serve as protection against complement-induced cell lysis. The underexpression of these proteins can be associated with autoimmune haemolysis.¹¹⁷ Even though many associations have been made, still no conclusions have been drawn regarding antigen specificity of antierythrocyte antibodies.

Clinical findings and establishing diagnosis

AIHA can be diagnosed in a stepwise manner. First, the anaemia must be established as haemolytic, which can be ascertained by serum biochemistry of haemolytic markers (eg, haptoglobin, lactate dehydrogenase, indirect bilirubin), presence of reticulocytosis and by examination of the peripheral blood smear. Second, using direct antiglobulin test, the clinician should determine whether autoimmunity against red blood cells is triggering haemolysis. Lastly, identification of the type of antibody responsible for haemolysis has to be defined. Warm-acting-AIHA and cold-acting-AIHA are based on the optimal temperature of antigen–antibody reactivity. This multitiered approach should lead to diagnosis or exclusion of the diagnosis of AIHA in patients with SLE.

Patients with AIHA present with constitutional signs and symptoms of anaemia, including fatigue and dyspnoea on exertion. Patients with SLE with AIHA can

have other concomitant autoimmune haematological manifestations. For example, patients with SLE can present with AIHA and thrombocytopenia concomitantly or sequentially, which is known as Evans syndrome.¹¹⁸ Patients with Evans syndrome may have frequent relapses, once glucocorticoids have been tapered or stopped. Hence, when a diagnosis of AIHA in patients with SLE has been established, monitoring for the development of thrombocytopenia is important.

Treatment

Glucocorticoid therapy is first-line treatment for AIHA. A majority of patients show a clear response to therapy (Hb >10 g/dL) within the first three weeks of treatment. Once response has been achieved, glucocorticoid should be tapered. About 10% of patients do not respond to this therapy and will require a second-line treatment.

Many drugs have been used as second-line agents. Patient eligibility criteria for second-line therapy have been proposed⁴³ (table 3). Still there is no general consensus on the best second-line agent. Drugs reported in the treatment of refractory AIHA in SLE include IVIG, azathioprine and other immunosuppressive medications as well as danazol and rituximab. A series of 26 patients with SLE from France with AIHA is informative.¹¹⁹ The aim of the study was to evaluate the response to treatment as well as the long-term outcome in a cohort of patients in whom severe AIHA was the primary SLE manifestation. Glucocorticoids were used as a first-line treatment in all patients. Oral prednisone (mean dose of 1 mg/kg) was used as the first-line treatment in 13 patients. The other 13 patients received high-dose methylprednisolone as an initial treatment. An initial response was obtained in 25 patients. Ten patients received hydroxychloroquine, five patients received azathioprine and five patients received one or several immunosuppressants for refractory AIHA. IVIG was given to two patients, and four patients underwent splenectomy. Seven patients experienced a relapse of AIHA. At the time of relapse, most of the patients were free of treatment or were receiving a low-dose glucocorticoid. Overall, 100% of the patients were in remission, which was complete in 85% of the patients. The authors concluded glucocorticoids were the treatment of choice and that splenectomy did not have a place in AIHA treatment. Patients refractory to the conventional

treatment can be treated with immunosuppressive drugs, danazol or rituximab.¹¹⁹ Hence, second-line treatment is not established and will vary from patient to patient.

Recently, treatment of AIHA with rituximab has been undertaken. Long-term safety and efficacy of B cell depletion with rituximab for AIHA in patients with paediatric SLE was assessed in a study by Kumar *et al.* Nine patients were included in the study, which suggested rituximab therapy is safe and efficacious, inducing long-term clinical remission.¹⁰¹ Similarly, in a case report, a patient responded to rituximab after exhaustive second-line treatment strategies failed.¹²⁰ Clinical and immunological response to rituximab treatment was evaluated in another dose-escalating study of rituximab for the treatment of SLE and Evans syndrome.¹²¹ Scheiberg *et al* also retrospectively evaluated patients with various autoimmune disorders who were refractory to other treatment modalities. This analysis favoured rituximab for both safety and efficacy.¹²² Although rituximab is a promising drug, multicentre randomised controlled trials are required to establish long-term optimal dosing, efficacy and safety of this drug for AIHA in patients with SLE who are refractory to other second-line treatments. Unfortunately, because AIHA is an uncommon manifestation, such trials are not likely forthcoming.

Summary

AIHA is one of the common aetiologies of severe anaemia in patients with SLE. Reports regarding its diverse clinical presentation and heterogenous association to other autoimmune manifestations make prompt attention essential. While glucocorticoids are used as first-line therapy in patients with SLE with AIHA, there are no high-quality data to guide second-line treatment. Rituximab is promising in refractory and non-responding AIHA.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Introduction

The description of presentation of a teenage girl by Moschowitz, in the early 20th century, drew attention towards this previously unnoticed disease affecting multiple organs.¹²³ Karl Singer, however, introduced the term thrombotic thrombocytopenic purpura >20 years later.¹²⁴ In 1964, Amorosi and Ultmann defined the

Table 3 Proposed criteria for use of second-line therapy in refractory systemic lupus erythematosus-associated haemolytic anaemia⁴³

Basis of criteria		Comment
Time based	No response to glucocorticoid in 3 weeks	Second-line therapy required
Dose based	>15 mg/day of prednisone* for maintenance	Second-line therapy required
	15 mg/day to 0.1 mg/kg/day*	Second-line therapy encouraged
	<0.1 mg/kg/day	No second-line therapy

*Or the equivalent of 15 mg of prednisone.

classic pentad of clinical features of TTP, namely thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), neurological symptoms and signs, renal symptoms and signs, and fever. The evidence favours an autoimmune aetiology in many patients.¹²⁵ The association of TTP and SLE has been sporadically reported in the literature. These two separate clinical entities appear to run parallel on multiple fronts leading to diagnostic and management concerns.¹²⁶ TTP is not recognised as a criterion for classification of SLE.

Pathogenesis

The main pathogenic feature of TTP is the formation of platelet aggregates within the microcirculation.¹²⁷ An autoimmune aetiology is suggested based on multiple observations.¹²⁷ Occurrence of TTP in association with autoimmune diseases, especially SLE, is one piece of evidence for an autoimmune aetiology. Furlan *et al* investigated the prevalence of von Willebrand factor (vWF) cleaving protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13)) deficiency in patients with familial and non-familial forms of TTP. Familial deficiency was caused by a constitutional deficiency of the protease, whereas an inhibitor of vWF-cleaving protease was responsible in the non-familial TTP.¹²⁸ Tsai *et al* also studied the activity of ADAMTS-13 and sought inhibitors against this protease in the plasma of patients with acute TTP, patients with other diseases and normal subjects. Inhibitory activity was detected in 26 of 39 plasma samples from patients with TTP. The inhibitors were IgG antibodies.¹²⁹

Clinical features

TTP is clinically diagnosed based on the presence of characteristic features of fever, thrombocytopenia, MAHA with presence of schistocytes, neurological and/or renal impairment. There is considerable overlap between TTP and SLE regarding presenting features.¹²⁶ The traditional estimate for the diagnosis of TTP in SLE is 1–4%. Postmortem examination of patients with SLE by Devinsky *et al*¹³⁰ suggested even higher numbers of patients with this association. Also, different patterns of association have been suggested in various clinical reports. Although the diagnosis of SLE usually precedes that of TTP.¹³¹ There are instances of TTP preceding or occurring simultaneously with the diagnosis of SLE.¹³²

A study carried out in the Hospital for Sick Children in Toronto reported an association between childhood onset TTP and SLE. The clinical course of all five patients diagnosed with TTP from 1975 to 1998 was compiled. In addition, all childhood-onset TTP (ages 6–20) reported in the literature over the same period was reviewed. The clinical presentation of paediatric patients with TTP was similar to that observed in adults. Of the five patients initially diagnosed with TTP, three were diagnosed with SLE within three years and the other two patients fulfilled three ACR classification criteria for SLE within four years

of TTP onset. In total, 35 patients were selected from the review of literature, and of these, 9 fulfilled >4 criteria ACR criteria for SLE and 8 were found to have incipient SLE. The authors concluded that TTP in childhood is commonly associated with SLE.¹³³ Most recently, 5508 patients followed at the paediatric rheumatology unit of a university hospital from 1983 to 2010 were retrospectively reviewed. In total, 279 patients met the ACR classification criteria, and 2 of them had TTP.¹³⁴ Thus, these sets of data indicate that TTP in childhood may evolve to juvenile onset SLE.

TTP in association with SLE may portend more deleterious outcomes. Zheng *et al*¹³⁵ carried out a retrospective analysis on clinicopathological features and prognosis on eight patients with lupus nephritis complicated with TTP. All eight patients received immunosuppressive therapies and seven underwent apheresis therapy. These patients received plasma exchange and/or immunoabsorption. During a median follow-up of 12 months in seven patients, one patient died and only three patients had stable renal function.¹³⁵

Letchuman *et al*,¹³⁶ in their comparative study between January 2003 and December 2007 at Singapore General Hospital, also suggested SLE-associated TTP (sTTP) was more aggressive. Ten patients with idiopathic TTP (iTTP) and eight patients with sTTP were identified. But mortality was not different between the two groups (4/8, 50%, for iTTP; and 5/8, 62.5%, for sTTP).¹³⁶

Treatment

For half a century after Moschowitz's description of the disease, TTP remained untreatable. In the 1970s, John Byrnes and colleagues found that TTP could be treated by daily infusion of fresh frozen plasma.¹³⁷ However, plasma exchange has now replaced infusion of plasma as the therapy of choice. Rock *et al*¹³⁸ carried out a prospective randomised trial comparing plasma exchange with plasma infusion for the treatment of TTP in 102 patients. Outcome was analysed towards the end of first treatment cycle (day 9) and after 6 months. Plasma exchange was documented to be more effective than plasma infusion in the treatment of TTP after both cycles.¹³⁸

Plasma exchange remains the principal treatment for the patients with TTP in SLE. But high-dose glucocorticoid, cyclophosphamide and rituximab are also used in concert with plasma exchange in patients presenting with sequential or concomitant TTP in SLE. Several recent reports demonstrate the successful use of rituximab. A 52-year-old African-American woman was started on glucocorticoid and plasmapheresis after being diagnosed with both TTP and SLE. Her platelet counts continued to drop even after 10 rounds of plasma exchange. She was then started on rituximab, and after the second dose, her platelet counts were normalised. She was discharged on this drug as an outpatient.¹³⁹ Thus, refractory TTP with normal ADAMTS-13 responded well to rituximab.¹³⁹

Summary

TTP is a syndrome with diverse aetiologies that can involve a variety of pathogenic mechanisms. TTP and SLE are two separate clinical syndromes with overlapping features that can occur together either concurrently or sequentially. TTP in SLE may predict a less favourable outcome in regard to renal function. Treatment is plasma exchange, but rituximab may be useful in refractory disease.

MYELOFIBROSIS

Introduction

Myelofibrosis is characterised by clonal proliferation of myeloid stem cells accompanied by stromal production of fibrinous ground substance. These changes can be attributed to primary myeloproliferative disorders or can be a manifestation of various malignant, endocrine or inflammatory conditions.¹⁴⁰ Acknowledgement of myelofibrosis as an aetiology of peripheral cytopenias in association with SLE is something recent. Myelofibrosis is not established as a classification criterion for SLE. Through review of the available literature, we conclude that myelofibrosis is definitely an uncommon manifestation of SLE.

Pathogenesis

Burkhard proposed the interplay between the immune reaction and bone marrow in SLE in the mid-20th century.¹⁴¹ In the light of discovery of 'Hargaves cell' in the bone marrow, that is, the LE cell, Burkhard suggested an integrating role of bone marrow pathology as an aetiology of haematological manifestations in patients with SLE. He also hypothesised that the regularity of bone marrow being a target in such patients could be attributed to disturbed equilibrium between protein production by the plasma cells and its proteolytic breakdown. The understanding of the pathogenesis of myelofibrosis is evolving and is far from definite. A variety of malignant and non-malignant conditions likely cause myelofibrosis as a non-specific reaction. Fibrosis, in general, is an imbalance between collagen synthesis and its breakdown. Circulating immune complexes, and autoantibodies in SLE, act on the megakaryocyte Fc-receptors and release growth factors, platelet-derived growth factor and transforming growth factor- β , all of which are known to induce collagen production. However, no specific antibodies are produced in patients with SLE who have myelofibrosis.

Due to inefficient haematopoiesis in patients with myelofibrosis, foci of extramedullary haematopoiesis (EMH) can occur in any organ. Bone lytic lesions associated with EMH due to myelofibrosis were described in one patient with SLE.¹⁴² The lesions were not biopsied to conclusively prove the suspected aetiology. Osteolytic lesions, however, are rare, even in primary myelofibrosis.

Clinical presentation

There have been 30 published cases of myelofibrosis secondary to clinically established SLE, according to our

search (table 4), but only 29 had data. In total, 23 out of 29 patients were women, and 16 of 29 patients presented before 30 years of age. In contrast to SLE, primary myelofibrosis occurs mainly in middle-aged and elderly patients, the median age at presentation being 67 years. In 1969, the first two SLE-associated myelofibrosis were reported, both from Malaysia.¹⁴³ Subsequently, the majority of published cases are among Caucasian or Mexican-American women, followed by African-American and Arab patients. Hence, from the literature available, the ethnicity predominance cannot be determined conclusively.

Presenting symptoms attributable to progressive anaemia or thrombocytopenia were prominent in all patients (table 4). In total, 12 of 18 patients had a palpable spleen on examination. Among 28, 23 had a haemoglobin of <10 g/dL at presentation. Of these 23 patients, 7 presented with severe anaemia with a haemoglobin of <6 g/dL. The leucocyte counts were invariably diminished among all 29 patients.

In a prospective, cross-sectional analytical study among 41 patients with SLE and peripheral cytopenias, bone marrow was found as a target organ affected by immune mechanisms.¹⁴⁴ Of 41 patients, 20 had bone marrow abnormalities that were categorised into six groups. Hypocellularity was the predominant finding, affecting 10 of the 20 patients. Reticulin fibre was increased in bone marrow biopsies of five patients, but significant bone marrow fibrosis was found in one patient only. The

Table 4 Summary of the reported patients with systemic lupus erythematosus (SLE) with myelofibrosis^{140 142–144 146 147 164–177}

	Average or number	Range or number evaluated
Age	35	12–70
Sex	23 women, 6 men	
Ethnicity	European White=8 Asians=4 Black Americans=2 Hispanic Americans=3 Middle Eastern=3	
White blood cell (units)	4265	1200–7700
Haemoglobin (g/dL)	7.9	2.7–13.9
Platelets (no/mm ³)	62 000	1000–341 000
Duration (weeks from SLE Dx)	124	0–572
Splenomegaly	12	29
Antinuclear antibody positivity	27	29
GC responsive	17	25
Improved cytopenias	23	29
Deaths	8	28

GC, glucocorticoid.

authors concluded that bone marrow examination should be recommended among patients who do not have improvement in their peripheral cytopenia after conventional therapy. But this study also documents that myelofibrosis is an uncommon finding among patients with SLE even with low peripheral blood cell counts.¹⁴⁴

Bone marrow hypoplasia was found to be a common abnormality among 23 patients studied by Feng *et al*,¹⁴⁵ who found 9 patients had hypoplastic bone marrow. Interestingly, in this study of bone marrow histology, the patient population was either taken off cytotoxic drugs at least a month before the study or were never on these drugs. In another study on bone marrow biopsies from 21 patients, Pereira also concluded bone marrow to be a target organ in SLE with peripheral cytopenia, but only one patient had myelofibrosis.¹⁴⁶

Treatment

The main treatment for SLE-associated myelofibrosis is glucocorticoid. Most patients, 23 of 28 whose status was known through published literature, survived (table 4). Improvement in peripheral blood cells counts and gradual resolution on repeat bone marrow biopsies was found in 17 of 25 patients who underwent a repeat bone marrow biopsy. A 54-year-old woman¹⁴⁷ achieved improvement of her bone marrow architecture and normalisation of peripheral cell counts only after administration of high-dose IVIG therapy. These findings further establish bone marrow as a target site in patients with SLE.

An important advance in the understanding of primary myelofibrosis is the recognition of overactive Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway signalling. A significant fraction of patients have activating mutations in JAK, the most common of which is JAK2V617F.¹⁴⁸ These data led to clinical trials of the JAK inhibitor ruxolitinib. In randomised controlled clinical trials, this drug demonstrated efficacy with reduction of spleen size, decreased symptoms and increased life expectancy.^{149–151} Ruxolitinib was approved for therapy of myelofibrosis by the US Food and Drug Administration in 2012. Unfortunately, to our knowledge, ruxolitinib has not been used in SLE-associated myelofibrosis. Further, neither JAK sequence nor JAK/STAT signalling has been assessed in myelofibrosis in SLE.

Summary

Bone marrow abnormalities are common among patients with SLE and peripheral cytopenias. Myelofibrosis is well described but uncommon in such patients. If myelofibrosis is diagnosed early in the course of the disease, most of the patients have shown improvement in the bone marrow architecture. In contrast, well-established myelofibrosis may lead to death. In total, 8 out of 29 patients did not respond to the treatment and had drastic deterioration in their cell counts and eventually died as a direct result of myelofibrosis (table 4).

Given that routine bone marrow pathological examination as a diagnostic tool in SLE is not practical, studies of the role of MRI or isotope marrow imaging, in patients with SLE, especially those who decline repeat bone marrow biopsy, are desirable. Also, in patients who eventually do not respond to treatment, transformation of the marrow to acute leukaemia or other complications should be studied. Such advances may guide therapy to decrease mortality among this patient population.

CONCLUSION

Haematological abnormalities are common findings in patients with SLE. It is important to distinguish haematological abnormalities as either manifestation of SLE, consequence of SLE treatment or as a part of another blood dyscrasia. Our review considered neutropenia, lymphopenia, AIHA, thrombocytopenia, TTP and myelofibrosis. According to the literature, mild neutropenia is a common finding in SLE and requires no specific therapy. However, patients with severe neutropenia with opportunistic infection or the risk of such infection can be successfully treated with G-CSF. Severely low lymphocyte count may also predispose patients to opportunistic infections such that prophylactic therapy should be considered. However, specific therapy for lymphopenia in patients with SLE is not indicated. Many patients with thrombocytopenia as a manifestation of SLE can be watched without specific treatment, and the great majority of those requiring treatment can be successfully managed. AIHA is one of the common aetiologies of severe anaemia in patients with SLE. While glucocorticoids are used as first-line therapy in patients with SLE with AIHA, second-line treatments are undefined. TTP occurs with SLE, either concurrently or sequentially, especially among children with SLE. Myelofibrosis is well described but uncommon in patients with SLE. If myelofibrosis is diagnosed early in course of the disease, most patients show improvement in bone marrow architecture.

FUTURE DIRECTIONS: WILL BIOLOGICS CHANGE THERAPY?

As discussed above, rituximab is a useful drug in treating serious haematological disease in SLE. Belimumab is the first biological drug approved for use in SLE by regulatory agencies. The efficacy of this drug for the haematological manifestations of the disease has only begun to be evaluated. One study has combined the results of the two randomised placebo-controlled trials of belimumab in SLE and studied organ-specific domain response. This approach considers all haematological manifestations together, however. Among patients with no organ involvement at baseline, a significantly lower percentage had worsening of the haematology index in the belimumab 10 mg/kg group. However, there was no improvement and maybe even a worsening of the haematological index among patients with high serological activity at baseline.⁴² So, the response of the

individual haematological manifestations or for that matter a composite profile remains to be determined. Approval of belimumab may open a new era of therapy for SLE, similar to that opened when anti-TNF biologics were introduced for rheumatoid arthritis. There are a number of drugs in development that target B cells via CD20 or CD22, including but not limited to tabalumab, blisibimod, atacicept, ocrelizumab, and ofatumumab, as well as additional drugs targeting the BLYS pathway. Unfortunately, we do not find data concerning haematological complications of SLE and these new biologics.

Bortezomib is a proteasome inhibitor that is available for use in multiple myeloma. Animal data in SLE-prone mice suggest that this drug might be efficacious in SLE. Bortezomib reduces survival of antibody-producing plasma cells, a cell type not targeted by anti-CD20 biological therapy. Thus, bortezomib is theoretically an attractive candidate, but an SLE clinical trial of standard dosing for myeloma was recently withdrawn as there are important and serious side effects.¹⁵² Nonetheless, two case reports of treatment of patients with both SLE and multiple myeloma are of interest. One patient was treated with a modified lower dose regimen with disappearance of antinuclear antibodies and anti-Sm, and the SLEDAI dropped to zero. This included a resolution of lymphopenia.¹⁵² Another patient with SLE and myeloma was treated with higher-dose bortezomib. There was complete resolution of SLE-associated thrombocytopenia sustained for at least one year.¹⁵³

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