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Review

Management of immune cytopenias in patients with systemic lupus erythematosus — Old and new

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ABSTRACT

There are various immune cytopenias associated with systemic lupus erythematosus (SLE). The most common one is anemia; however, there are different etiologies for the anemia caused by SLE. Anemia could be due to chronic disease, secondary to renal insufficiency, blood loss, drug induced or autoimmune hemolysis. There are other very rare causes of anemia secondary to SLE which include red cell aplasia, aplastic anemia, and microangiopathic hemolytic anemia. Treatment of the anemia would be according to the cause. Leukopenia, neutropenia, and lymphopenia are hematologic complications associated with SLE, and in majority of cases no treatment is required. Thrombocytopenia is one of the complications of SLE and is usually treated by steroids. However, there are significant numbers of patients which will either not respond to or relapse after treatment. This article summarizes immune cytopenias seen in patients with SLE, and it also discusses management of these cytopenias.

Contents

1. Introduction

Hematological involvement is common in SLE and no specific treatment is necessary in mild asymptomatic cases but close monitoring of cytopenia is warranted in most patients. Any significant changes in previous stable cell lineage parameters are considered to be an indication of SLE flare, and will need evaluation and close monitoring. This evaluation should include a detailed medical history for possible drug-induced myelosuppression, and in addition to stopping all medications which interfere with bone marrow function. Symptomatic treatment including transfusion therapy is required in cases with more severe hematological abnormalities. For the past 50 years, no new medication has been approved by FDA for SLE. Corticosteroids are considered the first line of treatment in severe cases for decades, and are effective in about 80% of SLE patients with hematological abnormalities. However, significant number of SLE subsets is resistant to conventional therapy and has high mortality and morbidity rates. There are second-line drugs such as immunomodulators and immunosuppressors

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for corticosteroid-resistant cases, but there is no randomized controlled clinical trial for most of these drugs and their use is anecdotal. Majority of these drugs are nonselective and have substantial toxicity. Moreover, there is no general agreement on definition of flare, response, and resistance and it is hard to compare the response rate of different drugs. More effective and less toxic drugs without any overt adverse effect still remain to be discovered [1,2]. SLE is the most common cause (38–61%) of ICU admission among all autoimmune disorders and respiratory system is the most common involved organ [3]. In the next few paragraphs we will discuss the different hematologic manifestations of SLE and their treatments.

2. Autoimmune hemolytic anemia

Autoimmune hemolytic anemia (AIHA) with or without thrombocytopenia occurs in about 10% of SLE patients and is a common and serious complication in these cases [4–7]. The warm type AIHA, mediated by IgG antibodies reacting in body temperature is the predominant type in patients with SLE while cold agglutinin AIHA is mediated by IgM complement-fixing antibody, which reacts at 4 °C. Patients with overt hemolysis present with anemia, elevated reticulocyte count, low haptoglobin, increased indirect bilirubin, high LDH, and a positive direct Coombs' test. New technologies such as cytofluorometry and specific diagnostic monoclonal antibodies may help to find the triggers of AIHA [8]. Presence of hemolysis might herald a relapse or reactivation of SLE. Relapse to conventional therapy is very common, necessitating alternative therapeutic agents. In a retrospective study of 26 SLE patients with isolated AIHA, there was 96% initial response to steroids such as prednisolone and high dose methylprednisolone and 73% of patients were recurrence free in 15 years follow up [9]. Systemic corticosteroids, 1 mg/kg or more of prednisone per day, remain the mainstay of the treatment for AIHA. Parenteral administration of steroids is preferred in symptomatic patients and ill patients. Switch to oral prednisolone after initial improvement is routine management. The dose is maintained for at least 4 weeks and slowly tapered. Clinical response is usually evident within a week and stabilization of the hematocrit occurs in 30 days after the initiation of therapy.

Corticosteroid has an early effect on reticuloendothelial system with suppressing tissue macrophages, and in the long term reduces antibody production [10]. Most patients need maintenance therapy. Patients who are refractory to steroids may benefit from azathioprine. Traditionally, azathioprine, a purine analog, has been used for various clinical manifestations of SLE, and may have steroid-sparing effect [11]. However, there have been anecdotal evidences of its efficacy as a steroid sparing agent since 1960s and its use in autoimmune diseases at a dose of 0.5to 2.0 mg/kg has stood the test of time [12].

Danazol, a heterocyclic steroid, is another option for selected SLE patients with AIHA. Danazol can downregulate monocyte Fc receptor and increase resistance of RBC cell membrane to osmotic lysis. Different dosages, ranging from 200 mg to 1200 mg per day have been used in refractory cases to standard therapy. A combination of prednisone and danazol has been proposed as a first line strategy in refractory AIHA [13]. Danazol does not increase the risk of infection but has androgenic and masculinizing side effects [14,15].

Intravenous immunoglobulin (IVIg) is standard of care in selected some immune deficiency disorders, and different autoimmune states including myasthenia gravis, idiopathic thrombocytopenic purpura, and Guillain–Barre syndrome. IVIg blocks Fc receptor and regulates idiotype-anti-idiotype network. IVIg has been mostly used for lupus nephritis, but there are some case reports of using IVIg in other lupus manifestations with the best results in patients with SLE associated thrombocytopenia. In one study, 3 out of 5 patients with AIHA and SLE had clinical improvement with IVIg therapy [16]. Complete blood count (CBC), LDH, direct antiglogulin test (DAT), and serum total bilirubin should be checked before starting IVIg. IVIg has few side effects with potential added value of prevention of infections, but is short acting with temporary improvement. To prevent transfusion reaction with rashes and headaches, IVIg should be delivered slowly and uniformly. The issue of cost, limited duration of action and potential for transmission of infections remain the major barrier for its liberal use. Thromboembolic events, renal impairment, and lupus flare up are very rare side effects [17]. Some patients develop DAT, but there are only a few case reports of acute alloimmune hemolytic anemia. Self-limited leucopenia, neutropenia, and monocytopenia have been reported after using IVIg, and their clinical significance is not clear [18].

B cells are the main source of immunoglobulin and have an important role in autoimmunity. There is a large body of evidence that points towards loss of B lymphocytes tolerance a critical issue in SLE pathogenesis. It has been shown that targeting B lymphocytes with rituximab, a chimeric monoclonal antibody against the B cell-specific calcium channel CD20, is associated with depleting B cells from the body and lowering the circulating autoantibody levels. The drug eradicates pre-B and B cells without affecting plasma cells or hematopoietic stem cells, and effectively normalizes homeostasis of peripheral B cell disturbances. Therefore, the total serum immunoglobulin will not change with rituximab therapy. The speed of response varies in different patients. The majority would respond in 2–4 weeks, however in some patients response might take weeks and months before a maximal B cell depletion is reached. There is a possibility that some B cell subsets are less susceptible to rituximab, and responsible for incomplete B cell depletion. Persistence of elevated autoantibodies in some SLE patients may be related to existence of long-lived plasma cells. B cell reemergence starts after 6–9 months and is complete after about a year [19–21]. Rituximab has been used in different studies for refractory SLE patients with various results. In all of them, SLE patients were receiving conventional treatments without placebo control and patients had different degrees of severity. There is only one trial (EXPLORER study) that the efficacy and safety of rituximab were compared with placebo [22]. In one study, rituximab therapy led to the reduction of oral corticosteroid dose by 9.5 mg/day on average in responders with good tolerance rate after a mean follow up period of 8.3 months [23,24]. In an open-label, multicenter study of rituximab in 14 patients with active and refractory SLE, 9 of them had major or partial clinical response without major side effects [25]. In another open-label study of 24 patients of active SLE regardless of intensive immunosuppressive therapy, rituximab improved clinical condition of 23 patients with significant reduction of dsDNA antibodies and increase in serum C3 levels [26]. In a prospective study of 11 patients of active or refractory SLE, there was 100% response rate followed by a rapid B cell depletion in a median 24 months of follow up. Six patients achieved remission, and five had partial remission, but 7 out of 11 patients experienced recurrence of SLE after a median 12 months following stopping the treatment [27]. A retrospective review of 11 patients with refractory SLE treated with rituximab showed that 10 of 11 patients had initial response to treatment but SLE recurrence occurred at a median 6.6 months [28].

As mentioned above, the Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) was the only adequately powered, double-blind trial that tested rituximab versus placebo. Although EXPLORER study demonstrated that rituximab decreased B cells and anti-dsDNA autoantibody and increased C3 and C4 levels, it did not find any differences between rituximab and placebo in the primary and secondary endpoint over 52 weeks of treatment of patients with moderate to severe SLE [22]. Nevertheless, all of aforementioned studies show that rituximab has adequate safety profile. In EXPLORER study, most patients had non-renal, musculoskeletal, or mucocutaneous SLE, and EXPLORER did not cover hematological subset of SLE.

In a case report of rituximab use in an 18 year old girl with life-threatening AIHA and SLE, rituximab decreased B cells from peripheral blood and demonstrated hematological response. In this case, patient received intravenous immunoglobulin (IVIg) and one cannot exclude the possibility that IVIg could have contributed in a positive manner toward the hematological response achieved in this case [29]. In a

retrospective analysis of 36 patients with AIHA refractory to several treatments, the overall response rate was 77%. 61% achieved a complete response and 16% reached a partial response [30]. In another retrospective analysis of 53 patients with refractory AIHA treated with rituximab in Belgium, the overall response rate was 79% with 47% complete response and 32% of partial response rate [31]. Mild infusion reaction including hypotension and fever is the most common complication of rituximab, and incidence of serious infection is very low. Herpes simplex is the most common viral infection. Interstitial pneumonitis has been reported as a very rare complication of rituximab therapy that may happen after exposure to the drug or develop in combination with chemotherapeutic agents [32]. Immune mediated, reversible neutropenia as a complication of rituximab monotherapy or in combination with immunosuppressors is another rare side effect of rituximab, and there is no need of any specific therapy of most of these cases [33].

First introduced for solid organ transplantation, mycophenolate mofetil (MMF) has been used for refractory cases of SLE with hematological manifestations. MMF is a pro-drug that after hydrolization to mycophenolic acid (MPA) it reversibly inhibits inosine-5′-monophosphate dehydrogenase (IMPDH) which in turn depletes guanosine and deoxyguanosine nucleotides in T and B cells and inhibits their proliferation, adhesion, and autoantibody production. Mycophenolate mofetil has been successfully used as a steroid-sparing therapeutic agent in AIHA patients with refractory SLE in some case reports. Normalization of hemoglobin was achieved within 3–4 months and no relapse occurred in over 12 months follow up [34–36]. It has been suggested that AIHA is more prevalent in SLE nephritis and antiphospholipid syndrome, and MMF is effective in both conditions. MMF had a complete or good partial response in four patients with refractory AIHA with improvement of hemoglobin and hemolysis parameters [37]. In most of these case reports, MMF was tolerated well with some gastrointestinal and bone marrow side effects.

It has been reported that high dose cyclophosphamide may be beneficial in refractory AIHA. Cyclophosphamide is metabolized to its therapeutically active compound, phosphoramide mustard which is responsible for alkylation and crosslinking of DNA, and acrolein which induces bladder toxicity. While cyclophosphamide depletes B and T cells, primitive hematopoietic progenitors contain aldehyde dehydrogenase and resistant to its toxic effects. In a case series of 9 steroid dependent patients with severe refractory AIHA, 6 patients went into complete remission. Nausea, vomiting, alopecia, herpes zoster infection, myelotoxicity, and premature ovarian failure are common side effects of cyclophosphamide [38].

For cold antibody AIHA, avoiding cold exposure is part of the treatment, but usually it is a disease which is difficult to treat. IgM is the main autoantibody in cold AIHA and plasmapheresis might be of benefit as it is efficient in removing the IgM antibody from intravascular compartment. Blood transfusions should be avoided as much as possible, not only due to the general transfusion reaction risks but also because of the inducing iso-antibodies against red cell antigens in SLE patients. Splenectomy has a debatable benefit in SLE patients (see below) [10].

3. Transfusion therapy in AIHA

Autoantibodies can potentially mask alloantibodies, and make it difficult to find the appropriate red blood cell by compatibility testing. However, sometimes clinicians face patients with progressive or severe symptomatic AIHA and reticulocytopenia that transfusion therapy is necessary and can be life-saving. Importantly transfusion should not be delayed in such situations. Most alloantibodies are directed against the blood group systems of Rh, Kell, Kidd, and Duffy. Occasionally, diluting the serum can help to detect the alloantibodies, but it is a time consuming and difficult process most of the time. The transfusion rate should be slow with transfusing of small portions of blood [10,39]. Transfusions should also be avoided unless absolutely necessary as patients with autoantibodies are more likely to develop alloantibodies than patients without them.

4. Other types of anemia

Anemia of chronic disease is a frequent cause of anemia in patients with SLE. The pathogenesis is usually secondary to suppression of erythropoiesis by chronic inflammation [6]. Anemia is usually normochromic normocytic with a low reticulocyte count, elevated ferritin and low iron levels, and bone marrow iron is usually adequate. The major mediator of anemia of chronic disease is hepcidin which usually inhibits iron release from macrophages and absorption of iron from intestine, leading to reduced iron utilization by erythropoiesis. Serum erythropoietin is usually reduced to the degree of anemia present. The majority of patients would be asymptomatic and do not require any treatment. Symptomatic patients may benefit from a trial of agents that promote erythropoiesis. Two products are available in the USA: 1. Darbopoetin alfa, a molecule that stimulates erythropoiesis with a longer half life than conventional recombinant human erythropoietin. 0.45 mcg/kg per week is a typical dose, but doses of 6.75 mcg/kg every 3 weeks have been used in cancer patients successfully. 2. Epoetin alfa. 80–120 units/kg per week is the usual dose, and patients are assessed after one month of therapy.

Assessment of the efficacy of erythropoietin in patients with SLE and anemia of chronic disease showed a response rate of 58% [40]. Patients who did not respond to erythropoietin and had active inflammation could respond if CS switched off the inflammatory process (prednisone 1 mg/kg might be effective in alleviating the anemia secondary to chronic disease).

SLE is a well recognized cause of renal disease and anemia secondary to lupus nephritis may cause anemia in patients suffering from chronic renal impairment. Treatment of such a patient is the same as the treatment of any patient with chronic renal impairment, i.e. through use of erythropoietin enhancing agents as mentioned above.

Iron deficiency anemia secondary to blood loss through either gastrointestinal tract or from menorrhagia is common in SLE. Chronic gastrointestinal blood loss is usually secondary to medication used to treat SLE including both nonsteroidal anti-inflammatory medications and corticosteroids.

Aplastic anemia is a very rare complication of SLE, and also can be secondary to immunosuppressor medications used to treat SLE. The possible mechanism for the occurrence of aplasia in SLE is thought to be secondary to the presence of autoantibodies against bone marrow precursors [41,42]. Aplastic anemia responds to the same management as SLE but treatment is usually challenging. High dose corticosteroid therapy, danazol, plasmapheresis, cyclophosphamide, and cyclosporine have been tried in sporadic case reports with variable results. High dose intravenous cyclophosphamide had marked success in a case of SLE associated aplastic anemia. In this case report, hematologic parameters started improving after one week of a single injection of high dose intravenous cyclophosphamide and was normal after six months of treatment [43]. Cyclosporine A (CSA) therapy was successful in management of a case with lupus associated aplastic anemia refractory to pulse cyclophosphamide, and high dose prednisone. Two weeks after starting oral CSA, patient started improving and at three months all hematologic parameters were normal [44]. CSA is associated with renal toxicity and hypertensive side effects. It has been reported that plasmapheresis was successful in providing long term hematologic remission in two cases of aplastic anemia and SLE. Both patients had complement-dependent antibody against granulocyte and erythroid colony forming units, and dramatic hematological response and decrease in inhibitor titers occurred following the plasmapheresis [45,46].

Pure red cell aplasia (PRCA) is a rare disease and association of PRCA and SLE is even rarer. There are many different possible causes for the occurrence of PRCA in SLE. PRCA secondary to antibodies directed against erythropoietin or bone marrow erythroblasts are some of the potential mechanisms. T cell mediated suppression of hematopoiesis has been suggested as a mechanism of PRCA in SLE [47–49].

PRCA is more common in inactive SLE, and responds to corticosteroids within one to four weeks in most cases (60%) but besides refractory cases, recurrence rate is quite high [47,50]. Cyclophosphamide, danazol, MMF, IVIg, CSA, EPO, and plasmapheresis have been used among other therapeutic modules. Use of danazol combined by corticosteroids has fewer side effects comparing immunosuppressors [51]. IVIg is another therapeutic option for PRCA in SLE patients but it's a costly modality [52,53]. CSA has been reported effective in some cases of PRCA and SLE but it takes about 3 months for full response rate [54,55]. It has been suggested that T cell mediated suppression of hematopoiesis is the possible mechanism of PRCA in SLE and combination of CSA and MMF was useful in a patient refractory to corticosteroids [56].

5. Leukopenia

Leukopenia is common in SLE and usually is secondary to lymphopenia, neutropenia or combination of both. Eosinopenia and basophilopenia are rare and have lesser clinical significance. Lymphopenia is common and T cell lymphopenia is the most common type of lymphopenias, and absolute lymphopenia correlates with SLE activity and high DNA antibody titers. Lymphopenia per se can predispose to autoimmunity and can also be a consequence of disease activity in the setting of active SLE. Concomitant lymphopenia and thrombocytopenia are highly indicative of disease activity rather than as a cause for autoimmunity [57].

5.1. Neutropenia

Moderate to severe neutropenia (neutrophil count <1000/μl) is a rather uncommon hematologic finding in patients with systemic lupus erythematosus. Several mechanisms are responsible in inducing neutropenia; disease activity and drug toxicity are among the most important causes. A positive association between leukopenia, neutrophil clustering activity (NCA) and SLE disease activity is reported [58,59]. Neutrophil specific autoantibodies and accelerated apoptosis are probably the major cause of neutropenia in SLE [60,61]. Severe neutropenia albeit uncommon may cause life threatening systemic infections in patients with SLE.

Glucocorticoids remain the mainstay of treatment in case of leukopenia. Other immunosuppressants or immunomodulators are frequently used for their steroid sparing effect. Cyclosporine A reversibly inhibits T cell mediated immunologic responses, and has been used in an open clinical study of 16 patients with various SLE manifestations. Leukopenia was normalized in 5 patients after three months of CSA without any major infection or other side effects [62]. Recombinant human granulocyte colony stimulating factor (rhG-CSF) is the best available treatment, and was effective in SLE associated neutropenia and refractory infection in different studies. In an open clinical trial of 9 SLE patients with neutropenia, 12 cycles of rhG-CSF increased lymphocyte and neutrophil counts within 48 h [63]. In the same study, 3 patients developed disease flare and it has been recommended that usage of the minimum amount of rhG-CSF is necessary to keep neutrophil count just above the level of 1000/microl. In 4 patients with severe granulocytopenia secondary to SLE, rhG-CSF increased absolute neutrophil count (ANC) within 24 h of administration, and ANC normalized by day 5 [64]. Safety profile of rhG-CSF is generally good with transient bone pain being the most common side effect, but elevated uric acid, leukocytoclastic vasculitis, and disease flare up have been reported. It is prudent to start rhG-CSF at lowest effective dose to prevent flare ups [61].

Mycophenolate mofetil and B-cell depletion therapy with rituximab have been used in autoimmune leukopenia with conflicting results.

6. Thrombocytopenia

Thrombocytopenia is a common and important manifestation of SLE which has direct relation with its morbidity and mortality. It is mild to moderate most of the time and does not need any specific treatment. However, severe thrombocytopenia occurs in the context of active disease. There are growing evidences that show presence of at least two types of autoantibodies, anti GPIIb/IIIa, and anti thrombopoietin receptor (TPOR) antibodies are the major pathophysiologic mechanisms of thrombocytopenia in SLE. Of importance of these two different autoantibodies is thrombocytopenia of patients with anti TPOR antibody which is less responsive to IVIg. It has been suggested that on the basis of presence of one of these autoantibodies or both, there are two different subsets of SLE patients with thrombocytopenia [65].

Corticosteroids are the first modality of treatment in SLE associated thrombocytopenia, and about 20% of patients have long term remission. Intravenous pulse corticosteroid therapy is an alternative in unresponsive cases. However, the response is rapid and transient and some patients might need an alternative treatment. Relapse is very common upon the tapering of corticosteroids [66]. As you will find in our review here, alternative medical and surgical therapeutic options have various and debatable results.

IVIg has been extensively used in SLE associated thrombocytopenia, but does not lead to a cure. IVIg therapy is not dependent on circulating antiplatelet antibodies level, but it blocks FC receptors of phagocytic cells and thus leading to reduce destruction of platelets. In an open clinical study, one month after initial 5 days of IVIg therapy 5 out of 7 patients had more than 50% increase in platelet counts [67]. However, patients in this study had chronic stable thrombocytopenia, and the increase in platelet count was temporary and patients should receive maintenance therapy for about a year. On the other hand, IVIg in 3 patients with SLE associated thrombocytopenia had a rapid but temporary increase in platelet counts, and a limited value [68]. There are other case reports that SLE patients with thrombocytopenia had rapid increase in platelet counts after IVIg administration, but it had transient effects and platelet counts reduced after 3–4 weeks. Conceivably, corticosteroids can potentiate IVIg effects, and IVIg is a good choice in induction therapy of life-threatening hemorrhage in SLE patients with thrombocytopenia when there is a need for rapid increase in platelet counts [69,70].

Danazol is an immunomodulator which is an effective agent in resolving SLE associated thrombocytopenia refractory to standard therapy. However, its exact mechanism of action is not clear. Danazol is a useful medication in thrombocytopenic SLE patients, has steroid-sparing effect, well-tolerated and has mild side effects such as weight gain, rash, and virilization. However, pseudotumor cerebri, hepatic adenoma, and cholestatic hepatitis have been reported and serial liver function test is necessary in long-term usage [14]. In a non-controlled clinical trial of six SLE patients with thrombocytopenia, danazol normalized platelet counts in all six patients. Danazol had a corticosteroid-sparing effect in all six patients, but one patient had relapse while receiving danazol [71]. In a prospective study of danazol in 16 SLE patients with thrombocytopenia or Evans' syndrome refractory to corticosteroid, all patients had normal platelet counts after two months and remission persisted in an 18.2 months follow up [72]. In a retrospective study of 18 thrombocytopenic SLE patients treated with combination of corticosteroids and danazol for 20 months, 50% (9 patients) had sustained long-term response in a mean follow up of 28 months [73]. In a retrospective study of danazol treatment in 39 SLE associated thrombocytopenia, combination of corticosteroid and danazol was the most prescribed medications (73%) with lowest probability of discontinuation. In this study danazol had the best survival rate and less discontinuation comparing corticosteroids and cytotoxic drugs [74].

Cyclophosphamide is an alkylating agent that has been used in thrombocytopenic SLE patients with higher probability of response in splenectomized cases. Cyclophosphamide has steroid-sparing effect and at the same time can treat the underlying disease and major

organ involvements. In seven SLE patients with moderate to severe thrombocytopenia, monthly intravenous cyclophosphamide therapy normalized platelet counts after a mean of two doses. C3 levels return to normal and anti-DNA antibody levels decreased in most patients [75,76].

There are some case reports that mycophenolate mofetil is promising in normalizing platelet counts in refractory patients with SLE associated thrombocytopenia. The additional benefit of MMF is this medication may treat the concurrent diffuse proliferative lupus nephritis. In a patient with SLE, thrombocytopenia, and lupus nephritis with negative antiphospholipid antibody refractory to corticosteroids, azathioprine, and IVIg, MMF normalized platelet counts in four weeks and renal function improved [77]. In an open clinical study of six patients with autoimmune thrombocytopenic purpura with various underlying disorders, two patients had complete response, three patients showed good partial response, and one patient did not have any response to MMF [36]. In both studies, patients tolerated MMF well with minimal side effects.

Cyclosporine interferes with $CD4^+$ T cells and interleukin 2 production. Adding cyclosporine A significantly improved thrombocytopenia in two refractory SLE. Prednisolone in one case patient, and combination of prednisolone and cyclophosphamide in another patient did not improve adequately the SLE associated thrombocytopenia [78]. In a series of six refractory SLE patients with severe thrombocytopenia a complete response was observed in five patients in a mean 23.5 months follow up [79].

Rituximab is an anti-CD20 chimeric antibody that has been used effectively for B cell depletion in autoimmune and non-autoimmune disorders without significantly increasing the infection rate. In nine SLE associated thrombocytopenic patients refractory to corticosteroids and IVIg, all of them had rapid response to rituximab and platelet counts normalized within six months. However, two patients experienced relapse when rituximab stopped [80]. In a retrospective study of 40 heterogeneous groups of patients with primary and secondary immune thrombocytopenic purpura including SLE unresponsive to corticosteroids and IVIg, 28% did not respond to rituximab and 56.4% had complete response to therapy. The response was fast with median of 20 days, but the rate of sustain response was low and patients had high rate of relapse [81]. Azathioprine is also a well-recognized immunomodulator and is effective in improving platelet counts at a dose of 0.5–2 mg/kg [82].

Interleukin-11 (IL-11) is a proinflammatory cytokine with thrombopoietic growth factor activity which is produced by multiple tissues. IL-11 increases the number and maturation of megakaryocytes. In a case report of refractory thrombocytopenia with SLE, IL-11 was used for 5 days, and raised platelet count within 48 h [83]. IL-11 has significant side effects including fluid retention which can be a major issue in SLE patients.

7. Treatment of TTP in SLE patients

Thrombotic thrombocytopenic purpura is a life threatening thrombotic microangiopathy (TMA) that needs high index of suspicion in SLE. TTP can be divided to primary or idiopathic and secondary to an underlying disorder. Severe ADAMTS13 deficiency or presence of its inhibitor is a manifestation of acute idiopathic TTP, relapses are frequent, and plasmapheresis is the standard of treatment. In a large study of patients with connective tissue disorders and TMA the percentage of patients with TMA and connective tissue disorder who had severe deficiency of ADAMTS13 was only 16% versus 70% in the group with idiopathic TTP [84]. However, despite this difference in ADAMTS13 levels in the 2 groups clinical responses were similar. TTP is rarely seen with SLE, has higher mortality rate than idiopathic TTP, and usually is refractory to conventional therapy including plasmapheresis. Due to high mortality rate, TTP is the differential diagnosis of any SLE patient with thrombocytopenia and is challenging. There is no randomized clinical trial or guideline available for SLE associated TTP treatment, but combination of corticosteroids and plasmapheresis has been accepted as standard of care in these cases. There are emerging evidences that suggest that rituximab is an effective therapeutic measure in relapsing SLE associated TTP or refractory case to steroids and plasmapheresis. There is a rapid response to treatment and patients tolerate well [85–88].

Cyclosporine may have a role in refractory cases of SLE associated TTP. In a case of SLE with TTP refractory to corticosteroids and plasmapheresis, CSA improved platelet counts and decreased anti-DNA antibody titers within a month without any myelosuppression [88].

There are several case reports showing that adding cyclophosphamide to plasmapheresis and steroids is beneficial in SLE patients with TTP. Cyclophosphamide has added benefit of suppressing both SLE and TTP. Like any other patient with immunosuppressors therapy, patients who receive cyclophosphamide have increased risk of infections [89–93].

8. Splenectomy in SLE

Splenectomy is an invasive therapeutic modality and a frequent procedure for hematological manifestations of SLE but still the role of splenectomy in SLE associated hemocytopenia is not clear, and even some authors believe it is harmful. In one study, 30 unselected SLE patients with thrombocytopenic purpura and/or AIHA divided to two 15 groups of splenectomy and non-splenectomy and the result in a 19 months follow up for both groups were the same. However, cutaneous vasculitis, infections, and death rate were significantly higher in splenectomized group, and there is no long term benefit for splenectomy in SLE. It has been suggested that spleen is the place for clearance of circulating immune complex (CIC), and splenectomy might participate in SLE flare up, and lupus nephritis [94]. There are some case reports that splenectomy in SLE patients is associated with temporary improvement of cytopenia and patients had relapse after a short period of follow up [90]. In a study of 14 SLE patients with thrombocytopenia for a median duration of 12 months, the response rate of thrombocytopenia to splenectomy was not as good as idiopathic thrombocytopenic purpura. Remission rate of thrombocytopenia after splenectomy was 14% with a relapse rate of 79% in a median follow up of 1.8 years [95]. On the other hand, some authors believe that spleen is a major lymphoid organ and a place for removing immune complex coated cells and producing autoantibodies and SLE patients may benefit from splenectomy. In a study of 200 SLE patients who were followed for at least two years, 16.5% of them (33 patients) had thrombocytopenia. Nine of twelve patients with severe thrombocytopenia underwent splenectomy. Six patients achieved long term, complete remission while 2 of them had partial response without any SLE exacerbation suggesting that splenectomy has a place in SLE associated thrombocytopenia [96]. In another retrospective study, 3.1% of all patients with SLE had splenectomy, and 3.8% of all splenectomies were done on SLE patients. In 25 SLE patients with thrombocytopenia, 64% (16 patients) had complete response and 24% (6 patients) had partial response with 88% overall response while 12% (3 patients) did not have any response to splenectomy in 30 days post-splenectomy. In a median follow up of 6.6 years, thrombocytopenia improved in 84% of patients [97].

In a retrospective study of 20 SLE patients, thrombocytopenia in 18 patients and clinically significant autoimmune hemolytic anemia were the main indications for splenectomy. Of these patients with severe hemocytopenia and refractory to high dose steroids, 67% had immediate and sustained platelet response during the follow up period. In this study, authors considered splenectomy as an effective treatment for SLE associated hemocytopenia [98]. In another retrospective study of 16 (1.9%) splenectomized patients out of 860 patients with SLE, five patients continued low dose steroids and achieved normal blood counts. Eight out of 12 (67%) thrombocytopenic patients had excellent results in long term follow up [99].

We believe that as we progress in our understanding of cytopenias mechanism in SLE, it is prudent to add cyclophosphamide or rituximab to corticosteroids before proceeding with splenectomy, and splenectomy

Table 1
Major cytopenias in SLE.

Cytopenia	Type	Relative frequency	Key laboratory features	Management
Anemia	AIHA	Common	↑Retic, ↑LDH, ↓Haptoglobin +DAT	Cs, danazol, rituximab, IVIg, MMF, splenectomy, CYC
	ACD	Most common	NL MCV & MCH	EPO
	IDA	Common	↓MCV,↓ MCH	Iron supplementation
	Megaloblastic	Not rare	↑MCV, ↓ B12 & FA levels	Folate and B12 supplementation
	Aplastic	Very rare		Cs, danazol, CYC, CSA, Plasmapheresis
	PRCA	Rare		Cs, danazol, CYC, CSA, plasmapheresis, MMF, IVIg
Leukopenia	Lymphopenia	Very common	<1500/ μl	Cs, CSA, MMF, CYC, rituximab
	Neutropenia	Uncommon	<1000/ μl	rhG-CSF
Thrombocytopenia	Immune	Common	<150,000/ μl	Cs, MMF, CSA , IVIg, splenectomy, danazol, AZA, IL-11, rituximab, plasmapheresis
	Drug induced	Common	History	
	Infection	Not rare	Microbiology	
	TTP	Not rare	Schistocytes	
	APS	Not rare	APA	
	DIC	Rare		
	Marrow dysplasia	Rare		

ACD, anemia of chronic diseases; AIHA, autoimmune hemolytic anemia; APA, antiphospholipid antibody; APS, antiphospholipid antibody syndrome, AZA, azathioprine; Cs, corticosteroids; CSA, cyclosporine A; CYC, cyclophosphamide; DAT, direct antiglobulin test (Coombs' test); DIC, disseminated intravascular coagulopathy; EPO, erythropoietin; FA, folic acid; IL-11, interleukin-11; IVIg, intravenous immunoglobulin; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin, MCV, mean corpuscular volume; μl, microliter; MMF, mycophenolate mofetil; NL, normal; PRCA: pure red cell aplasia; Retic, reticulocyte count; rhG-CSF, recombinant human granulocyte-colony stimulating factor; TTP, thrombotic thrombocytopenic purpura.

should be considered if medical management of cytopenias fails. On the other hand, there are no clear criteria to predict which patient will respond to splenectomy. Major types of cytopenia in SLE and suggested treatments are summarized in Table 1. The novel therapeutic options which are more specific and less toxic may treat the underlying SLE and its other complications including lupus nephritis besides cytopenias.

Take-home messages

- Anemia of chronic disorder is the most common type of anemia in SLE but autoimmune hemolytic anemia with high reticulocyte count is a SLE diagnostic criteria. Glucocorticoids are the main treatment of AIHA and about 96% of patients have initial response to glucocorticoids but rituximab, cyclosporine, IVIg, and cyclophosphamide have successfully been used in selective cases.
- Transfusion may be problematic in AIHA, and even life threatening. Transfusion should be avoided and only be done cautiously and with a slow rate in highly selected patients.
- Lymphopenia is common in SLE and a sign of disease activity. Neutropenia is less common but may be associated with significant systemic infection.
- Thrombocytopenia is a common manifestation of SLE and has direct relation with its morbidity and mortality. Corticosteroids and rituximab are the mainstay of treatment but there are some emerging studies that show mycophenolate may be helpful in lupus-related thrombocytopenia.
- TTP is more common in SLE than general population and adding corticosteroid and cyclophosphamide to plasmapheresis shows better outcome. Rituximab has been used in relapsing or resistant SLE associated TTP.
- There are some anecdotal results in regard to necessity of splenectomy in SLE, but authors believe that in the new era of medicine and having biologic agents for SLE related cytopenia, splenectomy can have a role in selected pateints.

Disclosure

All authors do not have any conflict of interest to disclose.

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Anti-ganglioside antibodies are not useful as a serological marker of neuropsychiatric involvement in patients with systemic lupus erythematosus

Anti-ganglioside antibodies (AGA) have been proposed as putative serological markers of neuropsychiatric systemic lupus erythematosus (SLE), but recent findings are controversial. These autoantibodies are involved in the pathogenesis of several peripheral immune-mediated neuropathies. In order to investigate the potential role of AGA in neuropsychiatric SLE, Labrador-Horrillo et al. (**Lupus 2012;21:611-5**) tested the presence of AGA in the sera of a large cohort of consecutive SLE patients with or without active neurological involvement according to the 1999 ACR criteria for neuropsychiatric lupus syndromes. IgG or IgM AGA specific for different ganglioside antigens were detected by standard ELISA and confirmed by thin layer chromatography. AGA, mainly of the IgM isotype and specific for GM1 ganglioside, were exclusively found in about 30% of SLE patients with neurospychiatric involvement, but they did not correlate with any neurological manifestation in particular. Thus, the authors concluded that serum AGA are not useful as biomarkers of neurological complications in SLE patients.

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