Bone marrow abnormalities in systemic lupus erythematosus with peripheral cytopenia

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Abstract

Objectives

Peripheral cytopenia is frequently found among patients with systemic lupus erythematosus (SLE). Bone marrow examination is usually considered in most cases; however, the incidence and association between cytopenia and disorders of the bone marrow remain unclear. We therefore conducted a prospective, cross-sectional, analytical study among patients with SLE and peripheral cytopenia to determine the incidence of bone marrow abnormalities and to find predictive factors for bone marrow examination.

Results

Of the 41 patients, 20 had bone marrow abnormalities that could be categorised into six groups: hypocellularity (50%), plasmacytosis (35%), haemophagocytosis (30%), dyserythropoiesis (10%), aplastic marrow (10%) and myelofibrosis (5%). Most of the patients (75.6%) had moderate to severe, active disease and recovery from the cytopenia occurred after treatment of the SLE. None of the clinical factors was statistically proven to be associated with bone marrow abnormalities; however, 3 factors indicated an active disease status including (a) the SLEDAI score (b) the number of organs involved and (c) previous immunosuppressive drug therapy. All of these are potentially predictive factors of bone marrow abnormalities.

Conclusion

The incidence of bone marrow abnormalities is high among patients with SLE and peripheral cytopenia. Bone marrow may be one of the common targets of organs affected by immune mechanisms in active SLE. Peripheral cytopenia can be subsequently improved after treatment of the disease; therefore, bone marrow examination should be recommended among patients whose cytopenia does not recover after conventional therapy.

Key words

bone marrow, systemic lupus erythematosus, peripheral cytopenia

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Introduction

Peripheral cytopenia is a condition commonly found among patients with systemic lupus erythematosus (SLE), which, generally, is caused by various mechanisms, including immune-mediated cell destruction, immune-suppressive drug therapy, infections and disorders of the bone marrow (1). Previous studies demonstrated abnormalities in the tissue pathology of the bone marrow in these patients, for example hypocellular marrow, myelofibrosis, aplastic marrow, haemophagocytosis and dyserythropoiesis (2-11). Bone marrow examination will likely be considered in most of cases; notwithstanding, the incidence and relationship between peripheral cytopenia and bone marrow abnormalities remains unclear. We studied the bone marrow in patients with SLE and peripheral cytopenia to determine the incidence of disorders of the bone marrow and to determine which clinical factors indicate the need for a bone marrow examination.

Patients and method

This study was designed as a prospective, cross-sectional, analytic study conducted among adult patients with SLE at Srinagarind University Hospital, Khon Kaen, Thailand, between July 2009 and January 2011. Eligible participants were adult patients between 16 and 60 years of age with a diagnosis of SLE disease-according to the revised criteria of the American College of Rheumatology (ACR) (12,13) plus the presence of peripheral cytopenia – *i.e.* at least two of the following criteria (a) haemoglobin <10 g/dL, (b) white blood cells $<4x10^9$ cells/L, or (c) platelets $<100 \times 10^9$/L. The exclusion criteria were: pregnancy, patients with viral hepatitis or HIV infection, patients with cirrhosis or splenomegaly and patients who had an underlying haematologic disease. Clinical and laboratory data were collected to evaluate the activity level of the disease as per the score from the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (14).

Bone marrow examination

All of the patients underwent bone marrow aspiration and biopsy. The bone marrow specimens were stained with haematoxylin and eosin (H&E) and Gomori's stains. Reticulin fiber was graded from 0–4. Myelofibrosis was diagnosed if the presence of reticulin was over grade 3. Bone marrow cellularity was evaluated by comparing age-matched control bone marrow. Trained personnel performed all the bone marrow aspiration, biopsy and blood collection as per standard methods. All subjects gave their consent and the Ethics Review Board of the Faculty of Medicine, Khon Kaen University, approved the research protocol.

Statistical analysis

Continuous parameters were reported as the median and percentage. The proportion of patients in the normal *vs.* abnormal bone marrow groups was compared using the Fisher's exact test. Statistical analyses were performed with STATA version 10. A p-value <0.05 was considered statistically significant.

Results

Of the 48 eligible patients, 7 were excluded (six had viral hepatitis infection [four with hepatitis B and two with hepatitis C] and one was pregnant). Thus a total of 41 patients (39 females, 2 males) were evaluated. The median age was 30 years (range 17–55). The median duration of disease at time of enrollment was 5 years (range 0–23). The most common organ involvement was of the haematologic system, followed by kidney disease and skin lesion. The characteristic type of cytopenia was bicytopenia in 37 patients and pancytopenia in 4. Most of the patients (75.6%) had an active form of disease with an SLEDAI score of >3. Twenty-two patients (53.7%) had previously been treated with immunosuppressives (within a month before recruitment) and 75% of the patients were receiving low-dose steroid drugs. The clinical characteristics and laboratory data of the patients are summarised in Table I.

Bone marrow abnormalities were found in 20 patients (48.8%) and the disorders of the bone marrow findings could be classified into six groups (Table II). Hypocellular marrow was the most common bone marrow abnormality. As

Table I. Demographic and clinical characteristics of 41 SLE patients with peripheral cytopenia.

Characteristics	Patients (n=41)
Age, year (at enrolment)	
Median (range)	30 (17–55)
Sex, (%)	
Females	39 (95.1)
Males	2 (4.9)
Duration of disease, year	
Median (range)	5 (0–23)
Organ involvement, (%)	
Lupus nephritis	28 (68.3)
Skin lesion	9 (21.9)
Arthritis	5 (12.2)
Central nervous system involvement	4 (9.8)
Serositis	3 (7.3)
Gastrointestinal vasculitis	1 (2.4)
Haematologic involvement, (%)	
Lymphopenia	39 (95.1)
Autoimmune haemolytic anaemia	2 (4.9)
Characteristic of cytopenia, (%)	
Pancytopenia	4 (9.8)
Anaemia + Leucopenia	19 (46.3)
Anaemia + Thrombocytopenia	18 (43.9)
Activity of disease according to SLEDAI score, (%)	
No active disease (score <3)	10 (24.4)
Mild to moderate active disease (score 4–12)	22 (53.7)
Severe active disease (score >12)	9 (21.9)
Previous immunosuppressive drug, (%)	
Cyclophosphamide	16 (39)
Azathioprine	4 (9.7)
Methotrexate	2 (4.8)
No	19 (46.3)
Steroid dose, (%)	
Low dose (<15 mg/day)	31 (75.6)
Moderated dose (≥15 mg/day–<1 mg/kg/day)	3 (7.3)
High dose (≥1 mg/kg/day) or pulse methyl prednisolone	7 (17.1)

expected, sixty percent of the patients in this group had previously received immunosuppressive drugs within the month prior to entering the study, while the remaining patients (40%) had not received any immunosuppressive drugs.

Plasmacytosis – the second most common bone marrow deformity – was defined as 5% or more of plasma cells in the differential count of bone marrow. All patients in this group had active disease, and 60% of the occurrences co-existed with a systemic infection.

Haemophagocytosis was observed in six patients, two of whom had systemic infection without active disease and the remaining patients had moderate to severe flare ups of the disease. Moreover, in patients who presented with fever, a bone marrow stain for organisms and a bone marrow culture proved negative in all cases.

Dyserythropoiesis was only noted in two patients and presented without ringed sideroblast, dysgranulopoiesis, dysplastic feature of megakaryocyte and/or abnormal localised of immature precursors (ALIP). Both of these patients had an active disease and their cytopenia responded to treatment of SLE.

Aplastic marrow occurred in two patients; both of whom were new cases with severe, active disease and who had never received any immunosuppressives. Their peripheral cytopenia completely recovered following treatment with pulsed methylprednisolone.

Reticulin fibre increased in five patients: two with grade 1, two with grade 2 (but significant myelofibrosis ≥grade 3) and one with clinically active SLE without splenomegaly and negative for the JAKV617F mutation. A peripheral blood smear did not show a leucoerythroblastic blood picture or characteristic teardrop shape. Peripheral cytopenia was also reversed after immunosuppressive drug therapy in all five of these cases.

We categorised patients into three groups according to the severity of cytopenia: anaemia, leucopenia or thrombocytopenia (Table III). Most of the patients were in the severe anaemia group (46.3%), and seven from this group also had microangiopathic haemolytic anaemia and presented with lupus nephritis. Severe leucopenia was not found in our study, but most of our patients (87.8%) had mild leucopenia. All of the patients in the moderate leucopenia group had bone marrow abnormalities: most of those had mild thrombocytopenia and disorders of the bone marrow were not correlated to the severity of thrombocytopenia. We then further subdivided the patients within each group as mild, moderate or severe and summed them (Table IV). Most of the patients were in a severe cytopenia group and had more bone marrow abnormalities than patients in the mild cytopenia group (albeit not statistically significant).

Univariate analysis of the predictive factors indicating bone marrow abnormalities are shown in Table V. With this sample size, we did not find any one of the clinical factors alone was statistically associated with a disorder of the bone marrow. However, bone marrow abnormality is potentially indicated when all three factors which indicate active disease status are present, namely (a) SLEDAI score, (b) the number of organs involved and (c) previous immunosuppressive drug therapy.

Table II. Histopathological abnormalities of bone marrow in 41 patients with SLE and peripheral cytopenia.

Bone marrow findings	Patients
Abnormal bone marrow, (%)	20 (48.8)
Hypocellular marrow	10 (50)
Plasmacytosis	7 (35)
Haemophagocytosis	6 (30)
Dyserythropoiesis	2 (10)
Aplastic marrow	2 (10)
Myelofibrosis	1 (5)

Table III. Characteristics of peripheral cytopenia in 41 patients with SLE.

	Severity of cytopenia	Patients (n=41)	Bone marrow abnormalities
Anaemia, (%)			
Mild	(Hb 9–10 g/dL)	12 (29.26)	2/12 (16.66)
Moderate	(Hb 8–8.9 g/dL)	10 (24.39)	5/10 (50)
Severe	(Hb <8 g/dL)	19 (46.34)	13/19 (68.42)
Leucopenia, (%)			
Mild	(WBC 2–3.9 x 10^9 cells/ L)	36 (87.8)	15/36 (41.66)
Moderate	(WBC 1–1.9x 10^9 cells/L)	5 (12.19)	5/5 (100)
Severe	(WBC <1 x 10^9 cells/L)	0	–
Thrombocytopenia, (%)			
Mild	(Platelet 50–149 x 10^9/L)	34 (82.92)	16 (47.05)
Moderate	(Platelet 25–49 x 10^9/L)	4 (9.75)	3 (75)
Severe	(Platelet <25 x 10^9/L)	3 (7.31)	1 (33.3)

Table IV. Degree of cytopenia of 41 patients with SLE.

Degree of cytopenia	Patients (n=41)	Bone marrow abnormalities
Mild	8 (19.51)	2/8 (25)
Moderate	14 (34.14)	7/14 (50)
Severe	19 (46.34)	11/19 (59.21)

Table V. Univariate analysis of clinical predictive factors of abnormalities in bone marrow of 41 patients with SLE and peripheral cytopenia.

Variable	*p*-value
1. SLEDAI score	0.194
2. Number of organs involved	0.216
3. Previous immunosuppressive drug therapy	0.294
4. Severity of cytopenia	0.709
5. Lupus nephritis	0.742
6. Pancytopenia	0.756
7. Skin lesion	0.450

Discussion

The incidence of bone marrow abnormality is high among patients with SLE and peripheral cytopenia. Interestingly, most bone marrow abnormalities are found in patients who have a high SLEDAI score (indicating a moderate to severe, active disease) and their peripheral cytopenia recovers after treatment of the SLE. Accordingly, bone marrow may be one of the target organs affected by the immune-mediated mechanism; thus resulting in peripheral cytopenia in active SLE disease.

Hypocellular marrows are the most commonly observed abnormal bone marrow findings, *i.e*. representing fifty percent of all bone marrow histological features. Although almost 50% of patients in our study had received an immunosuppressive drug within the month of enrollment, the remaining patients had not received any drug; therefore, bone marrow proliferation may be inhibited by both autoimmune mechanisms and drug toxicity (15).

Haemophagocytic marrows were found in either active or inactive disease. This finding supports the theory that haemophagocytosis in the SLE patient can be triggered by both/either disease and/or infection (6, 7, 11).

Dyserythropoiesis was only noted in three patients; in contrast to the findings of Voulgarelis *et al*. (10), who reported dyserythropoiesis and dysmegakaryopoiesis in all cases. However, their inclusion criteria differed from our study as they recruited patients with neutropenia (PMN <1.5 x 10^9/L), which is less common and most episodes of neutropenia in SLE patients are associated with drug toxicity (16). Thus, dysplastic features in the neutropenic patient may be the result of previous drug therapy.

Aplastic anaemia occurred in two of our patients with severe, active disease. Our cases are similar to previous case series (4, 5) which demonstrated the recovery of peripheral cytopenias after methylprednisolone and immunosuppressive drug therapy. Our study also supports the hypothesis that haematopoietic progenitor cells may be suppressed by immune-mediated mechanisms which might then induce aplastic anaemia in SLE (4, 5, 15, 17).

Increased reticulin content was measured in five patients, but significant myelofibrosis was only found in one without also having the classic clinical signs and symptoms of primary myelofibrosis. The patient had moderate flare ups of SLE and also had an improvement of peripheral cytopenia following immunosuppressive drug therapy. This finding agrees with previous studies on myelofibrosis in SLE (9, 10, 18, 19). In our study, we found that immunologic factors were part of the pathogenesis of myelofibrosis in SLE. If the study sample size were increased, the clinical factors-the SLEDAI score, the number of organs involved and previous immunosuppressive drug therapy-might indicate associated bone marrow abnormality. Disease activity status may therefore be an important indicator of a bone marrow disorder.

The severity of peripheral cytopenia was not associated with disorders of the bone marrow. Although the patients in the severe cytopenia group were found to have more bone marrow abnormalities than those patients in the mild cytopenia group, the difference was not statistically significant with this sample size.

We conclude that the incidence of bone marrow abnormalities in patients with SLE and peripheral cytopenia is high. Most of the abnormalities were found in active SLE patients and the cytopenia improved after treatment of SLE. Bone marrow may be one of the common target organs affected by immune mechanisms, resulting in peripheral cytopenia. Standard treatment of the underlying disease should therefore be given before doing bone marrow studies, but a bone marrow examination should be recommended when peripheral cytopenias do not recover following conventional therapy.

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