Leukemia Research Reports 9 (2018) 58–64

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Systemic lupus erythematosus and myelofibrosis: A case report and revision of literature

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ARTICLE INFO

Keywords:
Systemic lupus erythematosus
Autoimmune myelofibrosis
Blood cytopenia

ABSTRACT

Blood cytopenia represents one of the diagnostic criteria for systemic lupus erythematosus (SLE) and may occur as the first symptom of the disease. Antibody-mediated peripheral destruction of blood cells is the main cause of cytopenia observed in patients affected by SLE, however, inflammatory anemia, nutritional deficiencies, immunosuppressive therapy and, more rarely, myelofibrosis (MF) have also been documented. In the literature, 45 cases of autoimmune MF (AIMF) and SLE have been previously reported. Here the 46th case of a 43-year-old female with a SLE and an underhand cytopenia, with a review of the literature.

1. Introduction

Hematologic disorders affect 85% of patients suffering from systemic lupus erythematosus (SLE) [1], so that peripheral blood cytopenia represents one of the diagnostic criteria for SLE [2,3]. In most of the cases, autoimmune haemolysis/leukopenia/thrombocytopenia, chronic inflammatory anemia and thrombocytopenia by anti-phospholipid syndrome occur, whereas myelofibrosis (MF) is rarely described [4]. MF is SLE has been associated both with neoplastic and autoimmune diseases [4]. Autoimmune MF (AIMF) is an uncommon hematologic disease characterized by anemia, bone marrow myelofibrosis, and an autoimmune feature [5]. The association between AIMF and SLE represents an extremely rare condition, with 45 cases previously described in literature [4]. Here we report the case of a 43-year-old female with SLE and an underhand cytopenia, with a review of the literature.

2. Case report

In November 2015, a 43-year-old female was admitted to the Surgery Department of our Hospital because of cholelithiasis with cholecystitis. During hospitalization, she developed fever, polyserositis, severe anemia (7.4 g/dl) and thrombocytopenia (27.000/mmc), so that she was transferred to our Department of Internal Medicine. Laboratory tests displayed anemia, thrombocytopenia and a marked increase of C reactive protein (20.7 mg/dl) and erythrocyte sedimentation rate (85 mm/h) values. An empiric antibiotic treatment with piperacillin-tazobactam was started leading to a progressive improvement of the abdominal symptoms and signs, as also documented by abdominal ultrasound and cholangio-MRI. However, fever and cytopenia persisted. Moreover, pericardial and pleural effusions worsened as demonstrated at echocardiogram and chest x-ray respectively. Infections and neoplasms were researched and ruled out. Considering polyserositis and cytopenia, autoantibodies were evaluated. Positive direct and indirect Coombs test and slightly positive antinuclear antibodies (1:40 homogeneous) were found, whereas all other autoantibodies were negative. In agreement with our haematologist, a bone marrow biopsy was performed showing: "Hypercellular bone marrow (70%) containing erythroid and myeloid elements and megakaryocytes showing hypolobated and hyperchromatic nuclei. A marked interstitial reticulin and collagen fibrosis (MF-3) was also evident (Fig. 1A,B). Immunohistochemistry for CD34 demonstrated rare immature hematopoietic precursors". JAK-2 mutations were negative. Moreover, abdominal ultrasound was repeated confirming cholelithiasis and showing only a slight increase of liver size, with no spleen enlargement.

During hospitalization, a progressive increase of creatinine serum values up to 3 mg/dl, anuria and anasarca occurred. Moreover, a 1.5 g/daily of proteinuria was documented. Urinary sediment test demonstrated hematic and hyalines cylinders with undone red blood cells. A renal biopsy was not done since a contemporary progressive decrease of platelet values (up to

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https://doi.org/10.1016/j.lrr.2018.04.004
Received 9 February 2018; Received in revised form 22 March 2018; Accepted 7 April 2018
Available online 10 April 2018

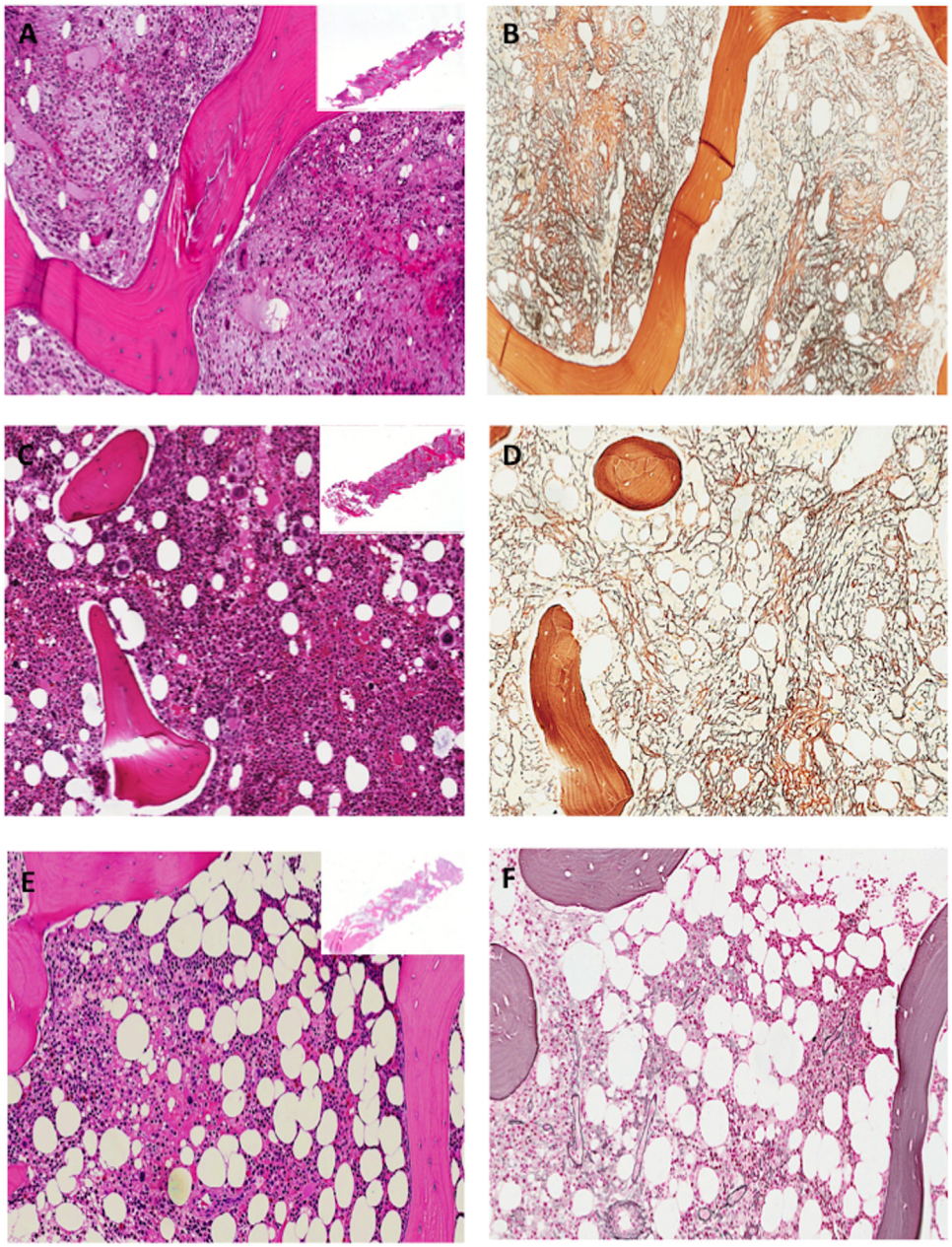

Fig. 1. Histology of consecutive trephine bone marrow biopsies (BMB). Pre-treatment BMB showed marked reticulin and collagenic interstitial fibrosis (MF-3) (A Haematoxylin and Eosin stain x100; B Gomori reticulin stain x100). During treatment BMB showed reduced collagenic interstitial fribrosis (MF-2) (C Haematoxylin and Eosin stain x100; D Gomori reticulin stain x100). Post treatment BMB showed regression of bone marrow fibrosis (MF-0) (E Haematoxylin and Eosin stain x100; F Gomori reticulin stain x100).

6000/mmc) occurred. Within 3 days patient's conditions become life threatening, thus considering renal dysfunction, positive Coombs test and ANA, a diagnosis of SLE was performed [1,3]. Autoimmune tests were repeated, confirming low titres ANA (1:80 homogenous) and showing a slight reduction of C3 and C4 complement fraction levels (C3 78 mg/dl and C4 9 mg/dl) and slightly positive anti dsDNA antibodies (1:20). Methylprednisolone 1 g iv/daily was started and continued for 3 days, obtaining a surprising fast and progressive improvement of clinical conditions and renal function. Azathioprine 50 mg/twice a day was also added achieving a gradual increase of peripheral blood cell count up to normal values. Within 3 months, the patients underwent to a progressive reduction of prednisone doses from 25 mg/daily to 10 mg/daily. After 6 months a bone marrow biopsy was repeated showing “hypercellular marrow (70%) due to myeloid and megakaryocyte proliferation with seldom hyperchromatic nuclei, decreased, reticulin fibrosis with focal formation of collagen bundles (MF-2)” (Fig. 1C, D). After one year of treatment, a follow-up bone marrow biopsy was further performed demonstrating a 30% cellular marrow and complete remission of bone marrow fibrosis (MF-0) (Fig. 1E, F). After 2 years follow-up, ANA are still positive (1:640), the patient is in good clinical condition, peripheral blood count is still within the normal range, 24-h proteinuria was progressively decreased up to values lower than 300 mg/24 h, no relapse of polyserositis was observed and no haematological diseases showed up. Maintenance therapy is still azathioprine 50 mg 1 cp twice a day and prednisone 7.5 mg/daily.

A literature search was done in PubMed, accessed via the National Library of Medicine PubMed interface (http://www.ncbi.nlm.gov/pubmed), using as keywords “systemic lupus erythematosus” and “myelofibrosis”. To our knowledge, only 45 cases of SLE and MF have been previously reported (Table 1**).**

Table 1
Autoimmune myelofibrosis in patients affected by systemic lupus erythematosus: review of the literature.

	Author,year	sex, age	autoantibodies	cytopenia	therapy	response	renal failure	other features
1	Lau, 1968[1]	F, 25	LE cells	pancytopenia	corticosteroid ns	PBC improvement No response at BMB	no	Fever, weakness
2	Cavalcant, 1978[2]	M,29	ANA,LE cells, ↓ complement	anemia	prednisone 60 mg/d	PBC e BMB improvement	no	none
3	Daly, 1983[3]	F,16	ANA,dsDNA ↓ complement	pancytopenia	Prednisone 30 mg/d Maintenance: prednisone 10 mg/d	PBC and BMB marked improvement	no	Weight loss, subcutaneous nodules, retinal exudates, Hemorragic features
4	Nanji,1984[4]	M,28	ANA,LEcell, dsDNA	Anemia, ↓platelets	corticosteroids ns	No response Patient died	Proteinuria 1.1 g/24 h	Fever
5	Kaelin,1986[5]	F,27	ANA,dsDNA, Coombs+, antiplatelet ↓ complement	↓ platelets	MTHYP 100 mg/6 h	PBC improvement No response at BMB	no	Hemorragic features
6	el Mouzan,1988[6]	F,13	ANA,dsDNA, LEcells, Coombs + ↓ complement	pancytopenia	prednisolone 30 mg/d	PBC improvement No response at BMB	no	Fever, anorexia, hemorragic features
7	Matsouka, 1989[7]	F,60	ANA, dsDNA LE cells, ↓ complement	Anemia, ↓platelets	Hydrocortisone 1 g/d	No response The patient died	↑ creatinine	Fever, weight loss, fatigue, hemorragic features
8	Inoue, 1992[8]	F,24	ANA,LEcells, antiplatelet ↓ complement	anemia, ↓platelets	MTHYP 1 g/d x 3 days then prednisone 1.2 mg/kg/d Maintenance: prednisolone15mg/d	PBC and BMB improvement	Proteinuria 1.8 g/24 h hematuria	Fever, hemorragic features
9	Foley-Nolan, 1992[9]	F,20	ANA, Coombs+ ↓ complement	Anemia, ↓ platelets	prednisone 60 mg/d plus azathioprine 150 mg/d	PBC and BMB complete regression	no	none
10	Borba, 1993[10]	F,39	ANA,RNP, Coombs+ ↓ complement	neutropenia	MTHYP 500 mg/d x 2d plus prednisone 10/ mg/d — Plasma exchange x 6 f plus MTHYP pulse and prednisone 20 mg/d, plus cyclophoshamide 100 mg/d	No response — PBC improvement No response at BMB	no	Fever, Raynaud phenomenon
11	Hirose, 1993[11]	F,54	ANA,aCL, LA ↓ complement	pancytopenia	MTHYP 1 g/d x 3d then prednisolone 60 mg/d	PBC and BMB marked improvement	no	Fever, weight loss
12	Fukuya,1994[12] Article in Japanese	F,54	ANA,aCL, LA ↓ complement	↓ platelets	MTHYP 1 g x 3d Prednisone 60 mg/d Maintenance prednisone ns	PBC complete regression and BMB improvement	no	Weight loss, fatigue
13	Paquette,1994[13]	M,68	ANA, ↓ complement	anemia, leukopenia	Prednisone 20 mg/d	PBC and BMB regression	no	Lung disease
14	Paquette,1994[13]	F,23	ANA, LEcells ↓ complement	Anemia, ↓platelets	Prednisone 50 mg/d	PBC improvement BMB nr	no	Pharyngeal ulcerations, retinal lesion
15	Paquette,1994[13]	F,27	ANA, Coombs+ ↓ complement	pancytopenia	prednisone 60 mg/d	PBC and BMB response		Hemorrhagic features, ↑lymph nodes
16	Paquette,1994[13]	F,56	ANA,dsDNA,LEcells ↓ complement	Anemia, ↓platelets	prednisone ns	PBC no response BMB nr	Proteinuria++++	Cutaneous vasculitis
17	Paquette,1994[13]	F,18	ANA,dsDNA, LEcells, Coombs+ ↓ complement	anemia, ↓platelets	prednisone 80 mg/d	PBC improvement BMB nr	no	Fever, hemorragic features, ↑ lymph nodes
18	Paquette,1994[13]	F,70	ANA,Coombs+ ↓ complement	anemia, ↓platelets	high doses prednisone	No response the patient died	no	Fever, hematemesis
19	Paquette,1994[13]	F,58	ANA,LEcells ↓ complement	pancytopenia	corticosterois. ns	No response The patient died	no	psychosis
20	Paquette,1994[13]	F,69	ANA,LEcells	anemia, ↓platelets	prednisone ns	BPC improvement BMB nr		petechias

(*continued on next page*)

Table 1 (*continued*)

	Author,year	sex, age	autoantibodies	cytopenia	therapy	response	renal failure	other features
21	Ramakrishna, 1995[14]	F,18	ANA,dsDNA,LAC, antiplatelet, Coombs +	anemia,thrombocytopenia	prednisone 75 mg/d — Relapse danazol, vincristine, colchicine and IVIG — prednisone 50 mg/d, vincristine plus colchicine	PBC Response to no response — PBC and BMB regression	no	Fever, weight loss, hemorragic features
			↓ complement					
22	Agarwal, 1995[15]	F,12	ANA	↓platelets	prednisone 2 mg/kg/d	PBC and BMB regression		Fever, hemorragic features
23	Aharon,1997[16]	F,54	ANA,dsDNA,aCL, SSA ↓ complement	pancytopenia	prednisone 80 mg/d for 3 weeks — IVIG 400 mg/Kg/d for 5 days Maintenance prednisone us dosages	No response — PBC and BMB regression	no	Fever, weight loss, abdominal pain, ↑lymph nodes
24	Konstantinopoulos,1998[17]	F,26	ANA,dsDNA, antiplatelet	Anemia, ↓platelets	Prednisolone 1.2 mg/kg/d	PBC and BMB improvement	no	Liver dysfunction
25	Vora,1998[18]	F,22	ANA	pancytopenia	Plasma exchange — MTHYP 1 g x 3d	No response — PBC and BMB improvement	no	Severe recurrent posterior scleritis
26	Kageyama,1999[19] Article in japanese	F,67	ANA,dsDNA ↓ complement	pancytopenia	Corticosteroids ns	No response The patient died	no	Liver dysfunction
27	Durupt, 2000[20]	F,29	ANA,dsDNA ↓ complement	pancytopenia	glucocorticoid 2 mg/kg plus cyclosporine 5 mg/kg	BPC improvement BMB nr	hematuria	Fever,
28	Kiss,2000[21]	F,18	ANA, aCL	pancytopenia	MTHYP 1 g/d x 3d then 2 mg/kg/d plus cyclosporin 3 mg/kg Azatioprine 50 mg/d — steroids 1 mg/kg/d	No response — PBC and BMB regression	no	Fever, weight loss, myositis
29	Aziz, 2004[22]	M,22	ANA ↓ complement	pancytopenia	prednisone 1 mg/kg/d	PBC and BMB regression	no	Fever, epistaxis
30	Pillai, 2009[23]	F,40	ANA, Coombs + ↓ complement	pancytopenia	MTHYP 500 mg x 5d then prednisone 60 mg/d then MTHYP1gx3d plus Ciclophosphamide 50 mg/d os Maintenance: prednisone 5 mg/d plus MMF	PBC improvement BMB nr	no	Fever, abdominal acute pain lethargy
31	Sacre,2009[24]	F,44	ANA,dsDNA	Anemia, ↓platelets	Prednisone 1 mg/kg/d plus IVIG	PBC improvement BMB nr	no	Lytic bone lesions
32	Sarkar, 2009[25]	M,45	ANA,dsDNA, Coombs +	pancytopenia	Prednisone 60 mg/d	PBC improvement BMB nr	no	Fever, hemorragic features
33	Wanitpongpun[a], 2012[26]	na	na	na	corticosteroids and immunosuppressive druga ns	Response		na
34	Hasrouni,2013[27]	F,36	none	anemia, leukopenia	Prednisone 60 mg/d — Relapse:pulse methylprednisolone, rituximab and MF — IVIG 1 g/kg x 2d	PBC improvement — no response — PBC response BMB nr	no	None
35	Hasrouni,2013[27]	M,44	ANA,dsDNA	anemia	IVIG and prednisone ns	PBC response BMB nr	no	Fatigue
36	Fechner,2014[28]	F,49	na	pancytopenis	Corticosteroids ns	PBC improvement, BMB nr	na	Osteolytic lesions, osteosclerosis

(*continued on next page*)

Table 1 (*continued*)

	Author,year	sex, age	autoantibodies	cytopenia	therapy	response	renal failure	other features
37	Chalayer, 2014[29]	F,17	ANA, SSA, RNP ↓ complement	neutropenia	Methylprednisolone 500 mg/d for 3 days plus HCQ plus prednisone 1 mg/kg — IVIG 30 g/d for 4 days Maintenance therapy HCQ	No response to — PBC improvement BMB nr		Fever, edema, psychosis
38	Kakar,2015[30]	F,38	ANA,dsDNA,SSA,RNP ↑ complement	pancytopenia	methylprednisolone iv 250 mg/d x 5 days then MMF (1.5 g)	PBC improvement BMB nr	no	chylous polyserositis
39	Pundole, 2015[31]	F,41	ANA,Coombs+ ↓ complement	Anemia, leukopenia and ↓platelets thereafter	Prednisone iv 1 g x 3 days then 60 mg oral prednisone then 20 mg oral prednisone Maintenance Prednisone 10 mg/d plus HCQ	Partial response PBC No response at BMB	no	Fatigue, cough, fever
40	Koduri,2016[32]	F,22	ANA,dsDNA, Sm,RNP, SSB. 1. ↓ complement	pancytopenia	prednisone 1.5 mg/kg/d	PBC and BMB improvement	no	↑lymph nodes
41	Koduri,2016[32]	F,23	2. ANA	Anemia, ↓platelets	prednisone 2 mg/kg/d then prednisone 5 mg plus HCQ	PBC improvement BMB: nr	no	Cough
42	Ungprasert,2016[33]	F,33	ANA,dsDNA ↓ complement	pancytopenia	Prednisone 60 mg/d Maintenance Prednisone low doses plus MMF	PBC improvement BMB:nr	no	Fatigue
43	Cansu, 2017[34]	F,39	ANA,dsDNA,aCL IgG ↓ complement	anemia, ↓platelets	Prednisome 1 mg/kg plus azathioprine 150 mg/daily	PBC improvement BMB nr	no	↑lymph nodes
44	Anderson,2017[35]	F,69	ANA,dsDNA,Coombs+, ↓ complement	anemia, lymphopenia	high dose corticosteroids then IVIG x 5 d	PBC improvement BMB nr	no	lethargy
45	Anderson,2017[35]	F,55	ANA,dsDNA, ↓ complement	pancytopenia	High doses corticosteroids, MMF, IVIG	No response the patient died	no	lethargy
46	Present case	F,43	ANA Coombs+, dsDNA slight ↓ complement	anemia, thrombocytopenia	Methylprednisolone 1 g x 3 d plus azathioprine 100 mg/d	PBC and BMB regression	1.5 g/24 h proteinuria Urinary casts ↑ creatinine	Cholelytiasis, cholecystitis, anasarca

ANA: antinuclear antibodies, dsDNA: anti double stranded antibodies; LA:lupus anticoagulant; aCL: anticardiolipin antibodies; PBC: peripheral blood cell count; BMB: bone marrow biopsy; MTHYP: methylprednisolone; IVIG:intavenous immunoglobulins; HCQ:hydroxichloroquine; MMF:mycophenolate mofetil; ns: dosages not specified; na: not available; nr: not repeated.

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3. Discussion

This case seems of particular interest, since face up the topic of cytopenia in SLE. Blood cell count decrease in SLE can be related to several conditions including autoantibody mediated peripheral blood cell destruction, inflammatory anemia, immunosuppressive therapy [4] and more rarely to bone marrow diseases, such as primary myelofibrosis, aplastic anemia, bone marrow metastases and AIMF [6]. Pathogenesis of AIMF remains incompletely understood. It seems to depend on a nonspecific response of fibroblasts to growth factors, such as platelet derived growth factor (PDGF), transforming growth factor β and epidermal growth factor, released by neoplastic or reactive cells in the marrow [6]. In patients affected by SLE circulating immune complexes may induce megakaryocyte to release PDGF by binding Fc receptors [7]. **Actually, in the literature AIMF occurred mainly in patients with active diseases, showing in 29/45 cases (64.4%) low complement levels and in 21/45 (46.6%) positive dsDNA (**Table 1**).** Despite the association of SLE and MF has been rarely reported, in routine bone marrow biopsies obtained from SLE patients, a reticulin fibrosis is found, suggesting that bone marrow can represent one of the target of the disease. [8]. Thus, it is likely that prevalence of AIMF in SLE is underestimated, mainly considering that AIMF responds to the immunosuppressive agents commonly used in treating SLE. Efficacy of **corticosteroids,** azathioprine, cyclosporine, mycophenolate mofetil and cyclophosphamide has been proven, whereas effectiveness of intravenous immunoglobulins and plasmapheresis is not established [4,9]. **AIMF generally well responds to treatment, with a mortality of 20% (9/45 cases reported). However, in the literature most of the patients (80%) showed a marked improvement or a complete normalization of peripheral blood count, whereas bone marrow response (evaluated in 31/45 patients after treatment) was observed only in 51.6% of cases (**Table 1**).**

AIMF is related to systemic autoimmune diseases, although it can also occur in the absence of any systemic manifestation [9]. **Differential diagnosis between AIMF and SLE can be difficult**, since they share some clinical and laboratory features, which sometimes overlap between themselves [9]. In the case here reported, anemia and thrombocytopenia represented the onset signs of a systemic autoimmune disease, with symptoms potentially related both to SLE and AIMF. Polyserositis and positive Coombs test, indeed, are included among diagnostic criteria of SLE, but could have also represented one of the autoimmune feature related to AIMF [9]. **In our case, renal failure with increased creatinine levels, 1.5 g/24 h proteinuria, low complement levels and positive dsDNA strongly supported the diagnosis of SLE.**

The first description of AIMF associated with SLE date back to 1968 and until now, there are 45 cases described in the literature (Table 1) [4]. AIMF often occurs in patients with a preceding diagnosis of SLE. However, more rarely, AIMF can pre-exist to SLE or can be diagnosed contemporary, as observed in our case [4,8,9].

Both neoplastic and autoimmune MF has been related to SLE [5,7–10], so that it seems of particular importance to perform an early diagnosis and to decide the appropriate treatment. Neoplastic forms of MF include PMF, chronic and acute myeloid malignancies, lymphoid neoplasms, mast cell disease and carcinomas metastatic to the marrow [7–9]. Clonal markers such as JAK2 can be helpful in distinguishing PMF from AIMF, although it is present in only 50–60% of the cases and a negative result do not exclude PMF [8]. Thus, we recommend performing bone marrow biopsy in SLE patients when causes of cytopenia are not completely clarified. PMF and other neoplastic forms of MF, indeed, are related to a high risk of mortality and need to an appropriate chemotherapy treatment up to allogeneic hematopoietic cell transplant [7].

In conclusion, this case focuses the attention on MF as possible cause of low peripheral blood cell count in patients affected by SLE. We wanted to suggest that prevalence of AIMF is underestimated since it share some clinical and laboratory features with SLE and generally respond to the immunosuppressive drugs commonly used in treating this systemic autoimmune disease. Moreover, neoplastic MF can also occur. Thus, we recommend performing bone marrow biopsy in SLE patients when causes of cytopenia are not completely clarified.

A written informed consent has been obtained from the patients.

Acknowledgements

The authors would thank Dr Gian Lorenzo Chiarion Casoni, UOC Medicina 3, Ospedale Sant'Andrea, Roma, Italy for clinical collaboration

Funding

This case report has received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to declare, including specific financial interests, relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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