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

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A B S T R A C T

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 46\textsuperscript{th} 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) \cite{1,2,3}, so that peripheral blood cytopenia represents one of the diagnostic criteria for SLE \cite{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 \cite{4}. MF is SLE has been associated both with neoplastic and autoimmune diseases \cite{4}. Autoimmune MF (AIMF) is an uncommon hematologic disease characterized by anemia, bone marrow myelofibrosis, and an autoimmune feature \cite{5}. The association between AIMF and SLE represents an extremely rare condition, with 45 cases previously described in literature \cite{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 ultrason 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\textsuperscript{*}. 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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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).

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 fibrosis (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).
### 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 |
|--------------|----------|----------------|-----------|---------|----------|--------------|---------------|
| Lau, 1968¹   | F, 25    | LE cells       | pancytopenia | corticosteroid m | PBC improvement | no            | Fever, weakness |
| Cavalcant, 1978² | M, 29 | ANA, LE cells, complement | anemia | prednisone 60 mg/d | BMB improvement | no            | none |
| Daly, 1983³   | F, 16    | ANA, dsDNA    | pancytopenia | Prednisone 30 mg/d | PBC and BMB marked improvement | no            | Weight loss, subcutaneous nodules, retinal exudates, Hemorrhagic features |
| Nani, 1984⁴  | M, 28    | ANA, LE cells, dsDNA | Anemia, platelets | corticosteroids ns | No response | Patient died | Proteinuria 1.1 g/24 h |
| Kaelin, 1986⁵ | F, 27    | ANA, dsDNA, Coombs+, antiplatelet | platelets | MTHYP 100 mg/6 h | PBC improvement | No response at BMB | |
| el Mouzan, 1988⁶ | F, 13    | ANA, dsDNA, LE cells, Coombs+ complement | pancytopenia | prednisolone 30 mg/d | PBC improvement | no            | Fever, anorexia, hemorrhagic features |
| Matsouka, 1989⁷ | F, 60    | ANA, dsDNA, LE cells, complement | Anemia, platelets | Hydrocortisone 1 g/d | No response at BMB | |
| Inoue, 1992⁸  | F, 24    | ANA, LE cells, antiplatelet | anemia, platelets | MTHYP 1 g/d x 3 days then prednisone 1.2 mg/kg/d | The patient died | Proteinuria 1.8 g/24 h | |
| Foley-Nolan, 1992⁹ | F, 20    | ANA, Coombs+ complement | Anemia, platelets | Prednisone 60 mg/d plus azathioprine 150 mg/d | PBC and BMB complete regression | no            | none |
| Borba, 1993¹⁰ | F, 39    | ANA, RNP, Coombs+ complement | neutropenia | MTHYP 500 mg/d x 2 d plus prednisone 10 mg/d | — | No response | Fever, Raynaud phenomenon |
| Hirose, 1993¹¹ | F, 54    | ANA, aCL, LA complement | pancytopenia | MTHYP 1 g/d x 3 d then prednisolone 60 mg/d | PBC and BMB marked improvement | no            | Fever, weight loss |
| Fukuyama, 1994¹² | F, 54 | ANA, aCL, LA complement | platelets | MTHYP 1 g/d x 3 d | PBC complete regression | no            | Weight loss, fatigue |
| Paquette, 1994¹³ | M, 68    | ANA, complement | anemia, leukopenia | Prednisone 20 mg/d | PBC and BMB regression | no            | Lung disease |
| Paquette, 1994¹³ | F, 23    | ANA, LE cells complement | Anemia, platelets | Prednisone 50 mg/d | PBC improvement | no            | Pharyngeal ulcerations, retinal lesion |
| Paquette, 1994¹³ | F, 27    | ANA, Coombs+ complement | pancytopenia | Prednisone 60 mg/d | PBC and BMB response | no            | Hemorrhagic features, lymph nodes |
| Paquette, 1994¹³ | F, 56    | ANA, dsDNA, LE cells complement | Anemia, platelets | Prednisone ns | PBC no response | Proteinuria ++ | |
| Paquette, 1994¹³ | F, 18    | ANA, dsDNA, LE cells, Coombs+ complement | anemia, platelets | Prednisone 80 mg/d | PBC improvement | no            | Fever, hemolytic features, lymph nodes |
| Paquette, 1994¹³ | F, 70    | ANA, Coombs+ complement | Anemia, platelets | high doses prednisone | PBC improvement | no            | Fever, hemolytic features |
| Paquette, 1994¹³ | F, 58    | ANA, LE cells complement | pancytopenia | corticosteroid m | No response | The patient died | |
| Paquette, 1994¹³ | F, 69    | ANA, LE cells complement | anemia, platelets | Prednisone ns | BPC improvement | No response | |

(continued on next page)
| Author/Year | Sex | Age | Autoantibodies | Cytopenia | Other Features | Therapy | Response | Other Features |
|------------|-----|-----|----------------|----------|---------------|---------|----------|---------------|
| Ramakrishna, 1995 | F | 14 | ANA, dsDNA, LAC, antiplatelet | Anemia, thrombocytopenia | Prednisone 75 mg/d | Complement | Not Response | Fever, weight loss, hemolytic anemia |
| Agarwal, 1995 | F | 15 | ANA | Anemia, thrombocytopenia | Prednisone 2 mg/kg/d | PBC and BMB regression | Fever, hemolytic anemia |
| Aharon, 1997 | F | 16 | ANA, dsDNA, aCL, SSA | Pancytopenia | Prednisone 80 mg/d for 3 weeks | Colchicine | No Response | Fever, weight loss, abdominal pain, lymph nodes |
| Konstantinopoulos, 1998 | F | 17 | ANA, dsDNA | Anemia, thrombocytopenia | Prednisone 1.2 mg/kg/d | PBC and BMB improvement | No Response | Liver dysfunction |
| Vora, 1998 | F | 18 | ANA, dsDNA | Anemia | Prednisolone 1.2 mg/kg/d | PBC and BMB improvement | Fever, hemolytic anemia |
| Kageyama, 1999 | F | 19 | ANA, dsDNA | Pancytopenia | Corticosteroids | No Response | No Response | Fever, abdominal pain, myositis |
| Durupt, 2000 | F | 20 | ANA, dsDNA | Anemia, thrombocytopenia | Prednisone 2 mg/kg plus cyclosporine 5 mg/kg | BMB nr | Fever, hemolytic anemia |
| Kiss, 2000 | F | 21 | ANA, aCL | Pancytopenia | MTHYP 1 g/d x 3d plus cyclophosphamide 50 mg/d | BMB nr | No Response | Fever, abdominal pain, myositis |
| Aziz, 2004 | M | 22 | ANA, LAC, antimitochondrial | Anemia, epistaxis | Prednisone 1 mg/kg/d | Complement | No Response | Fever, hemolytic anemia |
| Pillai, 2009 | F | 23 | ANA, dsDNA | Anemia, thrombocytopenia | MTHYP 500 mg x 5d then prednisone 1 mg/kg/d | BMB nr | Fever, hemolytic anemia |
| Sacre, 2009 | F | 24 | ANA, dsDNA | Anemia, thrombocytopenia | Prednisone 1 mg/kg/d plus IVIG | BMB nr | No Response | Fever, hemolytic anemia |
| Sarkar, 2009 | M | 25 | ANA, dsDNA, Coombs+ | Pancytopenia | Prednisone 60 mg/d | No Response | No Response | Liver dysfunction |
| Wanitpongpun a, 2012 | F | 26 | ANA | Anemia, leukopenia | Prednisone 60 mg/d | PBC response | No Response | None |
| Hasrouni, 2013 | F | 27 | ANA, dsDNA | Anemia, leukopenia | Prednisone 60 mg/d | PBC response | No Response | None |
| Fechner, 2014 | F | 28 | na | Pancytopenia | Corticosteroids and immunosuppressives | BMB nr | Fever, hemolytic anemia |

(continued on next page)
| Author, year | sex, age | autoantibodies | cytopenia | therapy | response | renal failure | other features |
|-------------|---------|----------------|----------|---------|----------|--------------|---------------|
| F. Del Porto et al. | 37 | 58-64 | Table 1 (continued) | |
| Chalayer, 2014 | F, 37 | 29 | ANA, SSA, RNP | neutropenia | Methylprednisolone 500 mg/d for 3 days | No response to Fever, edema, psychosis | no | |
| Kakar, 2015 | F, 38 | 30 | ANA, SSA, RNP | neutropenia | Methylprednisolone 500 mg/d for 3 days | ↓ complement | ↓ com | |
| Pundole, 2015 | F, 31 | 41 | ANA, Coombs+, platelets | anemia, leukopenia and ↓ platelets | Prednisone 1 g x 3 days then Partial response | PBC improvement | ↓ complement 60 mg oral prednisone then No response at BMB thereafter | 20 mg oral prednisone |
| Kakar, 2016 | F, 32 | 42 | ANA, SSA, RNP | anemia, ↓ platelets | Prednisone 1.5 mg/kg/d | PBC and BMB regression 1.5.7.24/h | ↑ creatinine, | |
| Ungprasert, 2016 | F, 33 | 43 | ANA, SSA, RNP | slight anemia, thrombocytopenia | Methylprednisolone 1 g x 3 d plus Cholelytiasis, cholecystitis, anasarca | PBC and BMB regression | ↑ creatinine, | |
| Cansu, 2017 | F, 34 | 44 | ANA, SSA, RNP | anemia, ↓ platelets | Methylprednisolone 1 g x 3 d plus | PBC and BMB regression | ↑ creatinine, | |
| Anderson, 2017 | F, 35 | 45 | ANA, SSA, RNP | anemia, lymphopenia | High doses corticosteroids then IVIG x 5 d | PBC improvement | No lethargy | |
| Anderson, 2017 | F, 35 | 46 | ANA, SSA, RNP | slight anemia, thrombocytopenia | Methylprednisolone 1 g x 3 d plus | PBC and BMB regression | ↑ creatinine, | |

ANA: antinuclear antibodies, dsDNA: double stranded antibodies, LA: lupus anticoagulant, aCL: anticardiolipin antibodies; PBC: peripheral blood cell count; BMB: bone marrow biopsy; MTHP: methylprednisolone; IVIG: intravenous immunoglobulins; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil; ns: 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. Polymyositis 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.

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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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