EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2016.011

Case Report

A rare cause of cytopenia in a patient with systemic lupus erythematosus: Autoimmune myelofibrosis

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Abstract

Hematological abnormalities are very common in the course of systemic lupus erythematosus (SLE). Myelofibrosis is a bone marrow disorder in which there is excessive fibrous tissue formation in the bone marrow. Various benign and malignant disorders can cause or be associated with a diffuse increase in the bone marrow reticular tissue. Some diseases such as infections, neoplasms, and autoimmune diseases may also induce bone marrow fibrosis (secondary myelofibrosis). Cytopenia from autoimmune myelofibrosis (AIMF) in SLE is a rare condition. Here we present a case of AIMF associated with SLE and aim to emphasize on the other cause of cytopenia in SLE.

Keywords: Autoimmune myelofibrosis, systemic lupus erythematosus, cytopenia

Introduction

Hematological abnormalities such as autoimmune hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia are very common in the course of systemic lupus erythematosus (SLE). All these findings are also included as classification criteria in the American College of Rheumatology (ACR 1997) and the Systemic Lupus Collaborating Clinics (SLICC 2012) classifications (1, 2). In addition, autoimmune myelofibrosis (AIMF) can be seen rarely in SLE (3). Here we present a case of AIMF associated with SLE and aim to emphasize on the other cause of cytopenia in SLE.

Case Presentation

A 39-year-old female patient was diagnosed with SLE with chronic polyarthritis, malar rash, anti-nuclear antibody (ANA) positivity, anti-double-stranded DNA (anti-dsDNA) positivity, and hypocomplementemia at 2007. Hydroxychloroquine (HCQ), methotrexate (MTX), and prednisolone were administered. Because of remission at the 23th month of MTX treatment, the drug was discontinued [in 2009, the white blood cell (WBC) count was 6500/mm^3, hemoglobin (Hb) level was 11.9 g/dL, platelet (PLT) count was 162.000/mm^3, and erythrocyte sedimentation rate (ESR) was 18 mm/h]. Eleven months later, her skin lesions flared-up. Then, prednisolone 30 mg/day was administered and the HCQ dose was increased (in 2012, the WBC count was 3100/mm^3, Hb level was 11.8 g/dL, PLT count was 126.000/mm^3, and ESR was 96 mm/h). One month later, the skin lesions regressed. Nine months later, her skin lesions flared again and prednisolone was restarted (in 2013, the WBC count was 3400/mm^3, Hb level was 11.9 g/dL, PLT count was 120.000/mm^3, and ESR was 41 mm/h). One and a half years later, lymphadenopathy (LAP) was detected in the left supraclavicular region (in Dec 2014, the WBC count was 6200/mm^3, Hb level was 12.1 g/dL, PLT count was 178.000/mm^3, and ESR was 89 mm/h). Cervical, thoracic, and abdominopelvic tomography showed pathological LAPs. LAPs were reported as reactive inflammatory processes in positron emission tomography/computed tomography (PET/CT) scan. Biopsies of cervical and axillary nodes were reported as reactive. Repeated laboratory findings were as follows (Oct 2015): WBC count 4900/mm^3, Hb level 9.7 g/dL, PLT count 57.000/mm^3, ESR 94 mm/h, C-reactive protein level 0.345 mg/dL, anti-ds-DNA level 2.24 (N: 0–1.1), complement (C)3 level 45.2 mg/dL (N: 90–180), C4 level 5.88 mg/dL (N: 10–40), and serum creatinine level 0.77 mg/dL. Lupus anticoagulant test was negative. Anti-cardiolipin IgG antibody was 28.5 GPLU/L (normal, 0–19 GPLU/L) and anti-cardiolipin IgM antibody was 1.73 MPLU/L (normal, 0–19 MPLU/L). Coombs' test was negative. Because of bicytopenia/pancytopenia, blood smear and bone marrow biopsy were performed. The blood smear showed anisocytosis, poikilocytosis, and a decreased number of thrombocytes, but no tear drop cells or leukoerythroblastic blood smear were seen. Bone marrow biopsy showed hypercellular marrow (70–80%) with focal lymphocytic infiltration, and megakaryocytes were quantitatively normal with grade 1–2 reticulin fibrosis. JAK mutation was not observed (laboratory test results during the follow-up period are given in Table 1). The patient was accepted as having SLE-related AIMF, and prednisolone 1 mg/kg and azathioprine (AZA) 150 mg/day were administered. PLT counts increased in the first month of treatment (WBC count 6100/mm^3, Hb level 9.9 g/dL, and PLT count 203.000/mm^3).

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Submitted: 20.02.2016
Accepted: 26.04.2016

Table 1. The patient's laboratory findings during the follow-up period

	2007 (at the diagnosis of SLE)	2009	2013	2014	2015 October	2016 January (at the diagnosis of AIMF)	First month after AIMF
Hemoglobin (g/dL)	10.5	12.3	11.9	10.9	9.4	9.7	9.9
WBC count (/mm^3)	3200	7300	3400	3900	4900	4100	6100
Absolute lymphocyte count	1200	1100	800	800	1000	1200	500
Absolute neutrophil count	1700	-	1700	2800	2000	2400	5500
Platelet count (/mm^3)	172.000	165.000	120.000	144.000	57.000	56.000	203.000
ESR (mm/h)	95	26	41	50	94	128	47
CRP(mg/dL) (0–0.8)	1.36	0.258	0.319	0.341	0.345	0.300	0.420
ANA	Positive	-	-	-	-	-	PositIve
Anti-dsDNA (0–1.1)	1.88	-	-	1.83	2.24	-	¬0.94
C3 (mg/dL) (N=90–180)	78.3	-	81	48	45.2	-	-
C4 (mg/dL) (N=10–40)	5.92	-	6.35	5.88	5.88	-	-
ENA panel	anti-Sm+	-	-	-	anti-Ro+	-	-
Proteinuria	Negative	Negative	Negative	Negative	Negative	Negative	Negative
LDH(IU/L) (n=135–214)	113	-	-	-	178	-	-
AST (IU/L) (n=0–32)	15	23	42	37	26	18	17
ALT(IU/L) (n=0–33)	13	21	40	22	22	10	10
Creatinine (mg/dL)	0.7	0.8	0.75	0.77	0.77	0.71	0.63
Clinical findings	Arthritis, malar rash	No symptoms	Malar rash, enantem	No symptoms	LAP, malar rash	No symptoms	No symptoms
Treatment modalities after evaluation of clinical and laboratory findings	HCQ MTX 10 mg/week Folic acid 5 mg/week	HCQ	HCQ Metil prednisolone 32 mg/day	HCQ	HCQ	HCQ Metil prednisolone 64 mg/day AZA 150 mg/day	HCQ Metil prednisolone 56 mg/day AZA 150 mg/day

SLE: systemic lupus erythematosus; AIMF: autoimmune myelofibrosis; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: anti-nuclear antibody; anti-dsDNA: anti-double-stranded DNA; Sm: smith; ENA: extractable nuclear antigen antibodies; C: complement; LDH: lactate dehydrogenase; AST: aspartate transaminase; ALT: alanine aminotransferase; HCQ: hydroxychloroquine; MTX: methotrexate; LAP: lymphadenopathy

Discussion

Hematological involvement is common in SLE. It is sometimes necessary to distinguish SLE from any other blood disorders. Bone marrow abnormalities such as myelofibrosis may be rarely seen and cause cytopenia in patients with SLE (3).

Myelofibrosis is a bone marrow disorder in which there is excessive fibrous tissue formation in the bone marrow. Various benign and malignant disorders can cause or be associated with a diffuse increase in bone marrow reticulin fibrosis. Primary myelofibrosis (PMF) is a myeloproliferative neoplasm arising de novo (primary). It is characterized by clonal myeloproliferation, abnormal release of cytokines, and dysregulated kinase signaling (4). However, some diseases such as infections, neoplasms, and autoimmune diseases may also induce bone marrow fibrosis (secondary myelofibrosis). The natural history of PMF is that of limited overall survival, whereas autoimmune AIMF typically follows a benign course and responds well to steroids and/or other immunosuppressive agents (5). Because the treatment and the prognosis are so different, it is extremely important to distinguish between the 2 forms. The association between myelofibrosis and autoimmune disorders was first described in 1978, but Paquette et al. (6) first proposed the term "AIMF" in 1994. The current diagnosis of primary AIMF includes the presence of all of the following: reticulin fibrosis of the bone marrow, lack of clustered or atypical megakaryocytes, lack of myeloid or erythroid dysplasia, eosinophilia or basophilia, lymphocyte infiltration of the bone marrow, lack of osteosclerosis, absence of or mild splenomegaly, presence of autoantibodies, and absence of a disorder known to cause myelofibrosis (5-7). Most reported cases of AIMF have been associated with underlying autoimmune disorders such SLE, Sjögren syndrome, rheumatoid arthritis, autoimmune hepatitis, and antiphospholipid syndrome (3, 5).

In a case series, myelofibrosis was found in only 5% of 41 SLE patients (8). Myelofibrosis can develop before or after the diagnosis of SLE. The clinical presentation of myelofibrosis is heterogeneous, but most present with symptoms related to anemia or splenomegaly or with constitutional symptoms. It mainly affects elderly patients. Chalayer et al. (9) reviewed 28 cases of SLE-associated myelofibrosis. Among 28 patients, 25 patients were

female and the mean age was found to be 36 years. It can be rarely seen in males (10). In a study by Chalayer et al. (10), 13 of 28 SLE patients developed bone marrow fibrosis, with the onset varying with a mean of 5 years. In our case, the patient developed AIMF 8 years after SLE diagnosis.

Cytopenia may change from bicytopenia to pancytopenia in AIMF patients (3, 9). In a study by Fayyaz et al. (3), 82% (23/28) of patients had an Hb level of <10 g/dL at presentation. Of these 23 patients, 7 presented with severe anemia with an Hb level of <6 g/dL. The average Hb level, WBC count, and PLT count were found to be 7.9 g/dL, 4265/mm^3, and 62.000/mm^3, respectively.

Chalayer et al. (9) reported that SLE patients with AIMF had 46% pancytopenia, 46% bicytopenia (anemia and/or leukopenia and/or thrombocytopenia), 42% splenomegaly, and 3.5% hepatomegaly. Our patient had bicytopenia (anemia and thrombocytopenia) and multiple lymphadenopathies. Her lymph node biopsy was reported as a reactive lymph node. This may be related to SLE.

Bone marrow biopsy findings are different between primary and secondary myelofibrosis. PMF is characterized by megakaryocyte atypia and clustering, accompanied by granulocytic hyperplasia and a concomitant decrease in erythropoiesis. In AIMF, bone marrow biopsy usually shows marrow fibrosis with increased reticulin fibers and fibroblasts, which is virtually indistinguishable from PMF. Invariably and most importantly, no dysplastic features were noted in any of the hematopoietic lineages, including the complete absence of bizarre-shaped megakaryocytes typically seen in PMF. Vergara-Lluri et al. proposed that specific morphologic criteria allow the distinction of AIMF from PMF. The grade of reticulin fibrosis in bone marrow is mild in AIMF, while it is moderate to severe in PMF (5, 9). Bone marrow findings in AIMF associated with SLE include varying degrees of cellularity in the bone marrow, particularly hypercellularity. All elements, including megakaryocytes, appear morphologically normal. Megakaryocytes are mostly increased and/or clustered, and focal or massive lymphocytic infiltration can be observed. In our case, bone marrow biopsy showed a hypercellular marrow with focal lymphocytic infiltration and normal megakaryocytes with grade 1–2 reticulin fibrosis. JAK-2 mutation was negative. With these findings, it can be interpreted that myelofibrosis is associated with SLE (AIMF).

In the bone marrow of patients with AIMF associated with SLE, megakaryocyte counts are often found above normal or normal. Therefore, thrombocytopenia may result at least partly from an increased destruction of PLTs rather than a decreased production caused by bone marrow fibrosis (9). In our case, thrombocytopenia was more prominent than the other series; megakaryocyte counts and morphology were normal in the bone marrow.

The pathophysiology of AIMF is unknown. The pathogenesis of bone marrow fibrosis remains incompletely understood, but appears to be a relatively nonspecific response of fibroblasts to underlying cellular abnormalities. It is postulated that circulating autoantibodies and immune complexes of SLE may stimulate the Fc receptors of megakaryocytes, resulting in the release of growth factors such as PLT-derived growth factor and transforming growth factor beta, which promote collagen synthesis and marrow fibrosis (11). Throughout the course of illness, complement levels and anti-dsDNA antibody levels were positive in our patient. It can be commented that immuncomplexes and autoantibodies may be responsible for AIMF in our case.

Hematologic abnormalities are common in SLE. AIMF, which is a rare cause of cytopenia, should be considered in the presence of cytopenia in an SLE patient, and these patients should be evaluated by cytogenetic analyses and bone marrow biopsy.

Ethics Committee Approval: N/A

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.U.C., H.U.T.; Design - D.U.C., H.U.T.; Supervision - D.U.C., C.K.; Resources - D.U.C., H.U.T.; Materials - D.U.C., H.U.T.; Data Collection and/or Processing - D.U.C., C.K.; Analysis and/or Interpretation -D.U.C., H.U.T.; Literature Search - D.U.C.; Writing Manuscript - D.U.C., H.U.T.; Critical Review - D.U.C., H.U.T., C.K.; Other - D.U.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study has received no financial support.

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