Aplasia eritroide aguda y amegacariocitosis por el lupus eritematoso sistémico

Systemic lupus erythematosus-induced acute erythroid aplasia and amegakaryocytosis

Rui Suzano[1], Juvenal Morais[2], José Fernandes[3], Judite Sachicumbi[4], Luis Caminal-Montero[5]

[1] Department of Internal Medicine/Systemic Autoimmune Diseases Unit. Hospital da Horta (Portugal)
[2] Department of Intensive Care Medicine. Hospital da Horta (Portugal)
[3] Department of Hematology. Hospital da Horta (Portugal)
[4] Department of Pathology. Hospital da Horta (Portugal)
[5] Department of Internal Medicine. Hospital Universitario Central de Asturias (HUCA) / Instituto de Investigación Sanitaria del Principado de Asturias (ISPA). Oviedo (Spain)

ABSTRACT

Background: Anemia and thrombocytopenia are common features in patients with Systemic Lupus Erythematosus (SLE). However, erythroid aplasia and amegakaryocytosis as the main physiopathological causes without other associated disorders have been rarely described.
Case report: We report a 29 y/o female with SLE presenting with severe anemia and thrombocytopenia due to a bone marrow immunological blockage. The patient, who initially refused transfusions, was successfully treated and had a very fast hematological response to steroids, immunoglobulin, plasma exchange, eltrombopag, and rituximab.
Discussion: This is an unusual case and it is possible that in this kind of patients plasma exchange associated with immunosuppressant therapy may lead to a faster, more effective, and sustained recovery of the hematological disorders.

Keywords: Systemic Lupus Erythematosus, erythroid aplasia, amegakaryocytosis, plasma exchange, immunosuppressive therapy.

BACKGROUND

About 10% of SLE patients may present a severe hematological crisis during the course of the disease, being the main mechanism of peripheral destruction of blood cells associated with the presence of circulating antibodies.[1] Hemolytic anemia related to anti-erythrocyte and/or antiphospholipid antibodies (anti-PLs) was reported in approximately 10% of the patients, and immune thrombocytopenia was reported in 10-40% mainly due to antiplatelet antibodies and/or anti-PLs.[2-6] Both cytopenias are more common when anti-PLs and other immunological SLE-related disorders, such as thrombotic thrombocytopenic purpura and disseminated intravascular coagulation, are present.

Besides these peripheral mechanisms, some histopathologic bone marrow (BM) abnormalities have been seen in up to half of the patients with SLE-induced cytopenias, such as necrosis, stromal alterations, hypocellularity, dyserythropoiesis, plasmacytosis, distortion of normal BM architecture, abnormal localization of immature cells precursors, aplastic marrow and myelofibrosis, suggesting that the hematopoietic system could also be a direct target in the disease. This impaired bone marrow function seems to be related to immune-complexes, cytokines, T and B lymphocytes, and autoantibodies.[3,7,8]

CASE REPORT

A 29-year-old Caucasian female was diagnosed with SLE. The patient presented alopecia, malar erythema photosensitivity, oral ulcers, arthritis, and laboratory findings of leukopenia/lymphopenia and positive antinuclear antibodies (ANA) at 1:640. Anti-dsDNA, anti-Sm, anti-SSa/Ro, anti-SSb/La, anti-RNP, and anti-PLs (lupus anticoagulant, anticardiolipin antibodies and anti-beta 2 glycoprotein 1) were negative. The rheumatoid factor was positive at 50 IU/ml and the anti-cyclic citrullinated peptide was negative. Complement levels were normal. The erythrocyte sedimentation rate (ESR) was 15 mm and C-reactive protein (CRP) was negative. Urinalysis showed no abnormalities. She was prescribed with hydroxychloroquine (200 mg orally once a day) and prednisone (5 mg orally once a day) and remained asymptomatic. The laboratory tests performed since then were normal.

She had a medical past of vitamin B12 anemia due to atrophic gastritis treated with IM cyanocobalamin once monthly. Thyroid and other gastrointestinal diseases were ruled out. The patient had a family history of autoimmune thyroid disease (grandmother, mother, and uncles) and celiac disease (sister).

Two years later was hospitalized with malaise, minor gingival hemorrhage, and spontaneous ecchymosis. At admission the patient was asymptomatic and, excluding malar erythema and cutaneous hemorrhagic features, her physical examination was unremarkable. She had no fever, no signs of major active bleeding, and no evidence of hepatosplenomegaly or lymphadenopathy.

There was no recent history of febrile illness or other SLE-related symptoms and the patient denied any exposure to drugs or toxins.

Laboratory results: leukocytes: $4x10^3$/µl (neutrophils: 78%, lymphocytes: 19%); Hb: 10 g/dl; erythrocytes: $3.5x10^6$/µl (MCV: 86 fl; MCHC: 33 g/dl); reticulocytes: 0.4%; indirect and direct Coombs´ test: negative; platelets $1x10^3$/µl. INR and aPTT were at normal intervals; fibrinogen: 73 mg/dl (normal: 200-400). ESR: 28 mm; CRP: negative. ANA 1:1.280. Anti-dsDNA, anti-Sm, anti-SSa/Ro, anti-SSb/La, anti-RNP, and anti-PLs remained negative. Erythropoietin: 318 mIU/ml (normal range: 4.5-29). Transferrin, ferritin, and serum iron were within normal limits. Folic acid: 2.9 ng/ml (normal range: 3.0-17) and vitamin B12: 130 pg/ml (normal range: 180-900). Serum complement (C3, C4, and CH50), haptoglobin, TSH, biochemical analysis (electrolytes, liver, and kidney function), as well as serum IgA, IgG and IgM, were

Correspondencia: lcaminal@yahoo.es
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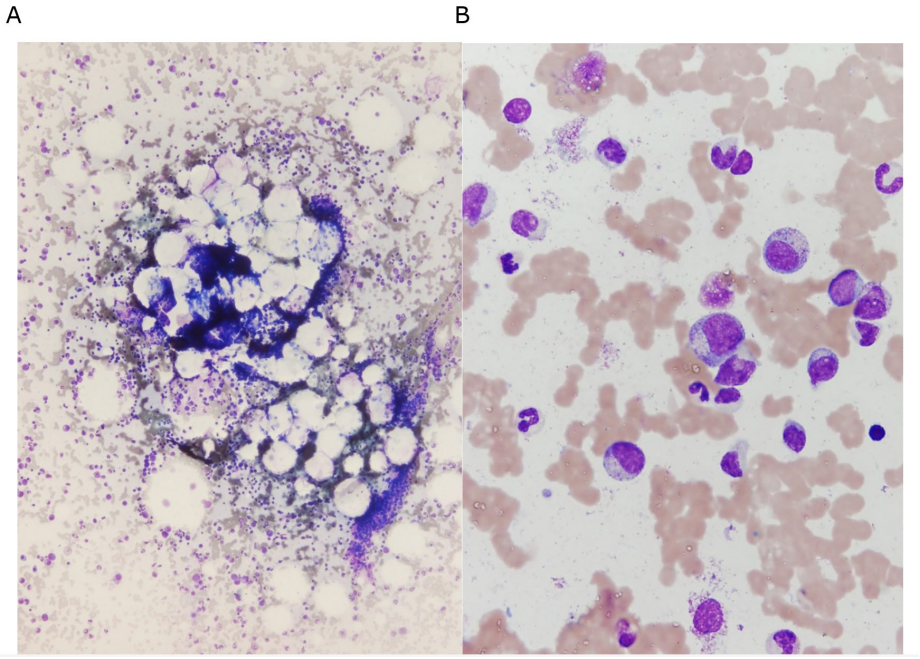
Photo 1 - Bone marrow cytology: Lack of erythrocytes and platelets precursors (May-Grunwald-Giemsa: A x 10 and B x 100).



normal. Anti-platelet and circulating immune-complex antibodies were negative. Urinalysis showed no abnormalities. IGRA and VDRL were negative and acute infections by the Epstein-Barr virus, CMV, hepatitis B, C hepatitis, HIV, and parvovirus B19 were excluded. A computed tomography of the chest and abdominal ultrasonography were not noteworthy. Peripheral blood smear showed low red blood cells and reticulocytes count, low platelet count without platelet aggregation, normal white blood cell count, and absence of megaloblastosis, schistocytes, or atypical forms. BM cytology revealed a complete absence of megakaryocytes and erythroid cells, preserved myeloid (~80%), lymphoid (~18%), and plasmacytoid (~2%) precursors, with no findings of myelofibrosis or atypical cells (Photo 1). Even though the bone biopsy was not performed, a diagnosis of SLE-induced marrow failure was considered.

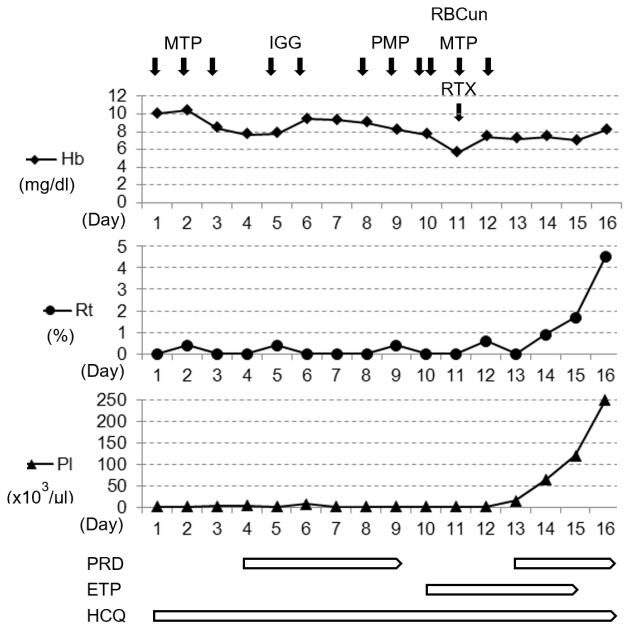
IM cyanocobalamin and oral folic acid were prescribed. Fibrinogen IV was also administered in order to reach the normal range. Hydroxychloroquine was maintained and she initiated a cycle of methylprednisolone (1000 mg IV once a day for 3 days) followed by prednisone (1 mg/kg orally once a day) and human immunoglobulin (2 g/Kg IV given in 2 days). She was then submitted to plasmapheresis (one daily session for 3 days) followed by the second cycle of methylprednisolone, rituximab (1000 mg IV), and eltrombopag (50 mg orally once a day for 6 days). No major bleeding, no other complications or clinical exacerbations of SLE were reported. Twelve days after admission, platelets and reticulocytes count increased and she was discharged four days later with hydroxychloroquine and prednisone (Graphic 1). Two weeks after discharge, blood analysis showed Hb: 11,5 g/dl, reticulocytes: 4%, and platelets: 180x10^3/µl. A second dose of rituximab was given, azathioprine was prescribed (2 mg/Kg orally once daily) after the rituximab, and prednisone was tapered to 7,5 mg per day. Due to gastric intolerance azathioprine was replaced by mycophenolate mofetil (2 g daily for 6 months and 1 g daily for another 6 months).

Three months later the blood cell count was normal (Hb: 12,5 g/dl; leukocytes: 6.5x10^3/µl and platelets: 260x10^3/µl); twenty-four months later she remain asymptomatic with normal blood cell count and prescribed with hydroxychloroquine (200 mg orally once a day) and prednisone (5 mg orally once a day).

DISCUSSION

Only less than 5% of patients with SLE present severe anemia (Hb<8 mg/dl) or severe thrombocytopenia (platelets <20x10^3/µl) and it is rare to find BM failure of autoimmune origin as the main cause.[1] The etiology of this autoimmune process is unknown. However, in some patients red cell aplasia seems to be related to inhibitory autoantibodies against erythroid progenitor cells, proerythroblasts, erythropoietin and the erythropoietin receptor. Additionally, amegakaryocytosis probably mediated by T cells and antibodies against thrombopoietin and the thrombopoietin receptor (anti-c-Mpl), has been described in a very small subset of SLE cases. [3,6,9-11] In our patient, neither the anti-erythropoietin antibodies nor the serum thromboplastin levels or the anti-c-Mpl antibodies could be evaluated but the lack of erythrocytes, and platelets precursors in the bone marrow aspirate, in the absence of other causes, along with high levels of serum erythropoietin strongly suggested an immunological blockage of the BM.

The optimal treatment of SLE-related autoimmune anemia and thrombocytopenia has not been yet defined. Steroids remain the cornerstone of therapy for severe active disease, associated with human immunoglobulin, cyclophosphamide, azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine, hydroxychloroquine, rituximab, belimumab, antithymocyte globulin, and plasma exchange; eltrombopag is a therapeutic option for thrombocytopenia and splenectomy can be considered as a last resource.[12-15] When BM is involved, con-



Graphic 1 - Evolution of hematologic parameters

Hb: hemoglobin
Rt: reticulocytes
Pl: platelets
MTP: methylprednisolone
IGG: human immunoglobulin
PMP: plasmapheresis
RBCun: red blood cell unit transfusion
RTX: rituximab
PRD: prednisone
ETP: eltrombopag
HCQ: hydroxychloroquine

ventional therapy with steroids and immunoglobulins not always has good results and even splenectomy may not be efficacious.[6] Moreover, recovery time can take several weeks or months and not all cases have a favorable outcome.

As our patient refused transfusions at the beginning of her treatment we decided to use more intensive therapy. The rationale for the treatment decision was to sequentially block the immune response with high doses of steroids and immunoglobulins, remove the circulating antibodies and immune-mediators through plasmapheresis and maintain the immunosuppression with rituximab, while stimulating the platelets production with eltrombopag. In fact, these measures allowed a very quick recovery of the severe and life-threatening hematopoietic disturbances, without any complications. In this particular situation, we considered that other commonly used immunosuppressant drugs such as cyclophosphamide or even mycophenolate mofetil were not a first-line option in the treatment of the acute phase due to their BM toxicity potential risk.

In conclusion, because direct involvement of the OM can be the cause of anemia and/or thrombocytopenia in patients with SLE, a cytological examination should probably be recommended in patients whose cytopenia does not recover after conventional therapy or presenting with severe hematologic disease with lack of evidence of red blood cell lysis. Plasma exchange associated with immunosuppressive therapy may lead to a more effective and faster recovery from the hematological disorder, and may be especially useful in patients who refuse transfusions.

PATIENT ANONYMITY AND INFORMED CONSENT
Not applicable.

DECLARATION OF CONFLICT OF INTEREST
The authors declared no potential conflicts of interest related to the research, authorship and/or publication of this article.

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