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Aplastic anemia in systemic lupus erythematosus: A better prognosis acquired aplastic anemia

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Introduction

Aplastic anemia (AA) is an uncommon hematologic manifestation of systemic Lupus erythematosus (SLE) with significant difference in the course and outcome from other forms of acquired AA due to underlying immune mediated mechanism of the disease. Here we report a case of SLE with thrombocytopenia at presentation and later evolved to develop pancytopenia with bone marrow aplasia.

Case report

A 58 year old lady was admitted to this hospital because of gum bleeding and low grade fever for 2 years with a history of recurrent oral ulcers, alopecia and Raynaud's phenomenon.

In 2014, she was evaluated in another hospital and found to have thrombocytopenia (platelet count 70 x 10^9/l) with positive antinuclear antibodies (ANA), anti-Ro (SS-A) and anti-RNP. A diagnosis of SLE was made according to ACR Classification criteria for SLE.[1] She was started on oral prednisone, however six months later her platelet counts started falling. On investigation complement levels (C3 & C4) were low. Bone marrow (BM) aspiration and biopsy was done which showed normoblastic erythroid hyperplasia. A three days pulse methyl-prednisolone 1 g/day followed by prednisolone 50 mg OD was started. However patient again developed thrombocytopenia when prednisolone was started tapering. This time oral eltrombopag 50 mg OD was added which was later stopped in 2015 with improvement in platelets.

In May 2016, she developed pancytopenia for which steroid dose was increased. She was transfused 3 unit packed red blood cells (PRBC) and 3 units random donor platelets (RDPs) and the dose of prednisolone was increased.

She came to this hospital with pallor, gum bleeding and low grade fever. On examination she had fundal hemorrhages. A complete blood count showed hemoglobin (Hb) 4.0 g /dl, total leucocyte counts (TLC) 1.2 x 10^9/l with absolute neutrophil counts (ANC) of 324 and platelets 4 x 10^9/l. A corrected reticulocyte count was 0.46 and direct coomb's test was negative, a repeat ANA was 2+ with speckled pattern and anti-Sm was positive. A BM aspiration and trephine was repeated which was hypocellular and consistent with aplastic anemia. paroxysmal nocturnal hemoglobinuria (PNH) was excluded by absence of PNH clones. HIV serology and polymerase chain reaction for CMV were negative.

Patient was transfused 4 units PRBC and 12 units of RDP, and was started on prednisolone 50 mg OD along with danazol 200 mg BD, however cytopenias did not improve. A three days of pulse methyl-prednisone 1 g /day was tried without any subsequent benefit. Finally she was started on oral cyclosporine 100 mg BD following which all three cell lineage started improving. At the time of discharge, Hb was 9.0 g /dl, TLC 3200 with ANC of 1344 and platelets 24,000.

Discussion

Hematological involvement is common in SLE and is often presenting manifestation of the disease. Hematological disorder is included in the SLICCC (Systemic Lupus International Collaborating Clinic) criteria for classification for SLE. This includes haemolytic anaemia or leucopenia (<4.0 x 10^9/l) or lymphopenia (<1.0 x 10^9/l) or thrombocytopenia (<100 x 10^9/l).[2]

The most frequent hematologic manifestation of SLE is anemia, usually normochromic normocytic, reflecting chronic illness. Aplastic anemia, however, is rarely reported, but in many cases, the role of concomitant drug therapy and secondary infections is confounding. BM examination is essential in cases of pancytopenia, particularly if the patient is receiving myelotoxic therapy such as azathioprine, mycophenolate mofetil or cyclosphosphamide. Specific features may present in the marrow to suggest drug-induced myelotoxicity. Azathioprine, for example, may cause aplastic anaemia, erythroid hypoplasia and megaloblastic changes. BM examination may also reveal hematological malignancy and hemophagocytosis.

Common abnormalities in the BM in patients with SLE include increased haemopoietic precursors suggestive of peripheral destruction or alternatively SLE induced hypocellularity, an increase in reticulin and a plasmacytosis.[3,4]

BM necrosis with stromal alterations is also frequently seen. Voulgarelis M et al. reported the BM findings of 40 patients with SLE and unexplained cytopenias: hypocellularity, necrosis, and stromal changes such as edema and fibrosis along with vascular changes were frequently present. BM was hypocellular in 58 % of patients, normocellular in 17 %, and hypercellular in 25 %.[5]

The mechanism of hematopoietic failure in SLE is immune-mediated. Autoantibodies, both complement dependent or independent were found to suppress both erythroid- and granulocytic-colony formation by hematopoietic Colony-Forming Units (CFU).[6-9] Autoreactive T cells were shown to inhibit CFU formation, damage hematopoietic stem cells through direct cytotoxic destruction, or induce apoptosis.[10]

Regarding the treatment of cytopenias, a detailed drug history and work up for seconday infection and hemophagocytic syndrome is essential. Immunosuppressive therapy is the cornerstone of the management of disease related BM failure. Systemic corticosteroid (oral prednisolone or pulse methyl-prednisolone) alone caused recovery in some cases, however most cases required further immune suppression.[11,12]

The use of plasmapheresis has been used successfully, aiming to remove auto-antibodies to BM hematopoietic precursors.[13-16] A dramatic response was seen after intravenous cyclophosphamide (0.5 – 1.0 gm /m2), usually one or two pulse therapy was sufficient[17-19] Supportive measures like transfusion of red cells and platelets, use of granulocyte colony stimulating factor and broad-spectrum antibiotics are an important part of management of aplastic anemia.

Reported cases of SLE associated BM aplasia showed better outcome than idiopathic acquired aplastic anemia which often has a poor outcome with a significant number of patients remains transfusion dependent and requires hematopoetic stem cell transplantation. This reflects the significant difference in the pathogenesis of the disease.

Conclusion

BM examination is utmost important in all cases of SLE with pancytopenia, severe or persistent leucopenia or thrombocytopenia. Conversely, in all cases of aplastic anemia, one should always look for clinical features of SLE and work up accordingly. Adequate immunosuppressive therapy can do wonder in this form of acquired BM aplasia.

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