

CASE REPORT

Myelodysplastic Syndrome as a Cause of Refractory Bicytopaenia in Systemic Lupus Erythematosus

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Citation: A Adenitan, KM Pindiga, H Olaosebikan, O Adelowo (2021) Myelodysplastic Syndrome as a Cause of Refractory Bicytopaenia in Systemic Lupus Erythematosus. J Rheumatol Arthritis Res 1: 103

Abstract

Haematological manifestations are frequently seen in systemic lupus erythematosus (SLE). Although mild cytopaenia is common in SLE, rarely are blood dyscrasias the presenting features of the disease. We report the case of a 49 years-old woman with background history of diabetes who presented with recurrent oral ulcers, worsening polyarthritis of the small joints of the hands, recurrent fever and progressive bicytopaenia. She fulfilled eight of the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE and was subsequently diagnosed with myelodysplastic syndrome (MDS) following recurrent bicytopenia (leucopenia and refractory anaemia) and a highly suggestive bone marrow feature. High-dose pulse methylprednisolone therapy, azathioprine, hydroxychloroquine and haemopoetic growth factors were unsuccessful in in lowering SLE disease activity and controlling bicytopaenia. She had a progressive downward course and died from fulminant septicaemia.

Keywords: Systemic Lupus Erythematosus; Myelodysplastic Syndrome; Bicytopaenia

Introduction

Systemic lupus erythematosus develops through many immunological mechanisms with the loss of self-tolerance and development of autoantibodies occurring sometimes many years before the onset of clinically evident autoimmune disease.[1,2] Hematological manifestations are commonly seen in patients with SLE .They usually result from an immune mediated bone marrow failure, excessive peripheral cells destruction or effect of drugs and infections.[3] Myelodysplastic syndrome (MDS) is characterized by abnormal haematopoiesis and a dysfunctional immune system .This Immune derangement contribute to the pathogenesis of MDS by causing cellular apoptosis.[4] Though rarely reported, the association between MDS and autoimmune diseases such as SLE has been described previously and such studies have suggested that antecedent autoimmune diseases may increase risk of MDS.[4] We report the case of a woman who following presentation and necessary investigations was found to have SLE and subsequently MDS. To our knowledge, there is no previous report of MDS presenting as a complicating feature of SLE in black Africa. We suggest that clinicians should be aware of this rare association in SLE. In order to gain more insight into the association of MDS and SLE, we examined relevant literatures as well.

Case Presentation

A 49-year-old woman who presented with 8 months history of recurrent oral ulcers, chronic inflammatory poly articular pain, fever, progressive body weakness and weight loss. There were no features of cardiac decompensation and other systemic review were not contributory. She is a known diabetes on metformin and glimepiride but denied a history of hypertension. She was admitted on several occasions on account of chest infection and recurrent anaemia that necessitated series of blood transfusions and use of various antibiotics. Because of recurrent and worsening bicytopenia despite being on treatment for SLE, further evaluation with bone marrow biopsy/aspiration was done and this led to the diagnosis of myelodysplastic syndrome. In spite of prednisolone dose of 30 mg/day and the patient remaining on azathioprine and hydroxychloroquine, the SLE remained active (SLEDAI-2K persistently >12) and there was persistent bicytopaenia. She was however continued on her oral antidiabetic agent metformin 1g twice daily which was occasionally converted to soluble insulin whenever patient presented with sepsis.

The clinical examination revealed a chronically ill looking middle aged woman who was pale, febrile 38.4^{c'}, with diffused non scarring alopecia, bilateral tender parotid enlargement, bilateral knee tenderness, synovitis of the small joints of the hands, multiple ulcers in the oral cavity, hepatomegaly and features of consolidation on the left upper hemithorax. The other aspects of systemic examinations were not remarkable. The baseline SLEDAI-2K disease activity was 12 indicating high disease activity.

Investigations

The complete blood count showed bicytopaenia as evidenced by anemia (Haemoglobin 4.5g/dl), and absolute leucopenia (total white cell counts $1.3 \times 10^9/L$). The white blood cells differentials and platelets counts were normal. The erythrocytes sedimentation rate was elevated to 120mm in the first hour (0-20mm/hr) and C-reactive protein was 127.7mg/L (0-7.2mg/L).

The bone marrow trephine biopsy demonstrated hypercellular marrow (figure 1) with cell to fat ratio 75:25. There was reversal of myeloid erythroid ratio with sequential maturation of all lineages and absence of hemophagocytosis. The bone marrow aspirate (BMA) showed few binucleate erythroblasts (figure 2) and reduction in myelopoiesis, there are also erythroid precursors with trilobed nucleus (figure 3). The blood film showed anisopoikilocytosis, leucopaenia with mild neutrophil left shift and pseudo-Pelger-Huët cells (figure 4) but no blast cells seen. Hyper segmented neutrophils with bizarre lobulation and hypo granularity (figure 5) was seen in the trephine biopsy. Normal Pel's stain also demonstrated in the trephine biopsy (figure 6). Megakaryopoiesis with few dysplastic megakaryocytes with separated nuclei (pawn ball megakaryocyte) (figure 7) and pseudo-Pelger Huët cells (figure 8) were also seen in the aspirate.



Figure 1: Section of trephine biopsy demonstrating hypercellular marrow with cell to fat ratio 75:25. There was reversal of myeloid erythroid ratio with sequential maturation of all lineages and absence of hemophagocytic cells.



Figure 2: Section of bone marrow aspirate showing few binucleate erythroblasts and reduction in myelopoiesis.



Figure 3: Section of bone marrow aspirate showing erythroid precursors with trilobed nucleus.



Figure 4: Section of peripheral blood film showing anisopoikilocytosis, leucopaenia with mild neutrophil left shift and pseudo-Pelger-Huèt cells but no blast cells.



Figure 5: Section of trephine biopsy showing hyper segmented neutrophils with bizarre lobulation and hypo granularity.



Figure 6: Section of Pels stain of trephine biopsy showing normal Pel's stain.



Figure 7: Section of bone marrow aspirate showing megakaryopoiesis with few dysplastic megakaryocytes with separated nuclei (pawn ball megakaryocyte).



Figure 8: Section of bone marrow aspirate showing pseudo-Pelger Huët cells.

The serology test revealed homogenous patterned antinuclear antibody (ANA) with a titre of 1:3200, elevated anti-dsDNA 38.4IU/ ml (0-12IU/ml), low C₃ 0.39g/l (0.9-1.8g/l) and normal C₄ 0.12g/l (0.1-0.4g/l) complements. The fasting blood glucose 9.6 mmol/l (2.5-6mmol/l) and glycosylated haemoglobin were elevated 6.5% (<6%). The other investigations were elevated serum ferritin 4346.2ng/ml (10-150ng/ml), normal serum iron 14.3umol/L (9-29umol/L), normal percentage iron saturation 39.8% (15-45%), normal serum folate 13.9ng/ml (3.1-20.5ng/ml), normal transferrin 2.43g/L (2.5-3.8g/L) and elevated vitamin B₁₂ 733pmol (133-675pmol/L). The lipid profile showed elevated total cholesterol 9.4mmol/L (2.5-5.2mmol/L) and triglycerides 12.8mmol/L (<2.29mmol/L), with overall picture showing dyslipidemia.

The serum electrolytes, urea and creatinine, urine albumin-creatinine ratio, urinalysis and liver function test values were all within normal limits. The HBsAg, HCV-antibody and retroviral screening were all negative while the GeneXpert was also negative for tuberculosis. The chest X-ray showed consolidative changes in the left apical zone while the results of electrocardiography, echocardiography and abdominopelvic ultrasound were not remarkable.

Treatment

The patient was commenced on intravenous pulse methylprednisolone 500mg daily for three days and subsequently on maintenance dose of prednisolone 30mg daily. She was also started on hydroxychloroquine 400mg daily and methotrexate 12.5mg weekly which was later changed to azathioprine 100mg daily when she was noticed to have consolidation due to community acquired pneumonia. She had three units of whole blood transfused to correct anaemia and was treated for the community acquired pneumonia with amoxicillin/clavulanic acid and azithromycin. Other supportive treatments included folic acid, omeprazole, calcium carbonate and vitamin D_3 . She later had pneumococcal vaccine when she was out of the acute phase. Although, she became stable and was discharged, she presented again after 3 weeks with features of severe anaemia and without significant improvement in her WBC, fluctuating between 1.0 x 10⁹/L and 1.5x10⁹/L. The anaemia was corrected and haemopoietic growth factors were commenced (filgrastim 300µg 3 times weekly and erythropoietin 4000iu 3 times weekly) with regular complete blood count monitoring. She was placed on atorvastatin 20mg nocte and prophylactic rivaroxaban 20mg daily. She was treated for oral thrush on two occasions with fluconazole and oral nystatin. The patient remained bicytopaenic and was admitted on two separate occasion on account of anaemia and sepsis from chest infection.

Outcome and Follow-Up

Within 2 weeks of pulse methyl prednisolone and subsequent tapering doses of oral prednisolone, there was significant clinical improvement. She was later discharged to continue on hydroxychloroquine and azathioprine. She was seen in the rheumatology clinic in a fairly stable condition, but she presented after 3 weeks of clinic follow up with features of severe anaemia and community acquired pneumonia. The patient was treated accordingly but had to have bone marrow biopsy and aspirate done following another presentation with anaemia and markedly low white blood cell count. She was commenced on haemopoietic growth factors and continued on hydroxychloroquine and azathioprine following the diagnosis of MDS. However, she developed overt features of febrile neutropenia and succumbed.

Discussion

The myelodysplastic syndromes are a collection of cytogenetically heterogeneous clonal bone marrow failure disorders derived from aberrant hematopoietic stem cells. Patients generally suffer from variably progressive and symptomatic bone marrow failure which may result in leukaemic transformation.[5] Using peripheral blood and bone marrow findings, MDS can be classified into subtypes which may have different etiologies where patients with autoimmune disease may be at increased risk of only some subtypes and not others.[6] A recent retrospective study in patients with established systemic autoimmune disease showed the following underlying MDS subtypes: refractory cytopaenia with multilineage dysplasia (31%), refractory anemia with excess blasts (15%), refractory anemia (14%), refractory anemia with ringed sideroblasts (12%), MDS with isolated del 5q (10%) and unclassi-

fied MDS (4%).[7] Another study showed that refractory anemia was the most common type of MDS (39%) in the ten large series and also among the 44 case series (36%) that were studied.[8] In addition, depending on the aetiologies, MDS can be classified as either a primary or secondary syndrome.[9]

Making diagnosis of MDS might be a little difficult especially in a background of autoimmune disease (AD). Though diagnosis is usually based on incidental blood count which shows minor changes in cell number and a blood film with characteristic abnormal cell morphology such as pseudo-Pelger Huèt cells and bizarre neutrophil segmentation. Sometimes, as in the index patient, a cause of persistent blood cell abnormality has to be actively looked for. Asides the clinical features of SLE, our patient presented with worsening leucopaenia, refractory anaemia and recurrent infections (septicemias). Infections are common in MDS patients. In one study, 10% of patients with MDS present with evidence of infection, and in another study it is the major cause of death in 21% of the patients.[10,11] Most infections in MDS are bacterial, usually with host organisms and associated with neutropaenia. In one series, 85 out of 141 patients had a neutrophil count <2.5x10⁹/l, but MDS differs from other causes of neutropenia in that not only is there abnormal neutrophil morphology such as bizarre hyper segmentation with hypo granularity as seen in the bone marrow of the index patient, there is also an associated defect of neutrophil function.[12]

About 85% of SLE patients have hematological manifestation during the course of their illness.[13] This is not surprising since blood and blood vessels together contain more diverse number of antigens than any other organ in the body and SLE autoantibodies are known to develop against any antigen or tissue.[14] Though there are reports suggesting that bone marrow may be targeted by SLE, rarely are failure of multiple cell lines as a result of bone marrow involvement a complicating feature of SLE.[13,15] It has been reported that about 10–30% of MDS patients may present with a variety of autoimmune disorder or their laboratory manifestations which could occur concomitantly, before or after the MDS diagnosis.[8,7] The connective tissue diseases account for 25-30% of MDS-related autoimmune diseases, with SLE contributing about 30%.[16] But reports on as to what extent the bone marrow is affected by SLE are limited as BMA and trephine biopsy were not done in most cases. This could be attributed to low index of suspicion when evaluating an autoimmune disease patient and limited laboratory facilities that could aid diagnosis. Our patient fulfilled eight of the SLICC classification criteria [17] and has bone marrow aspirate/biopsy that are highly suggestive of myelodysplastic syndrome-refractory cytopaenia with multilineage dysplasia. A study suggested that there was a statistically significant but small increased risk of MDS in patients with any autoimmune disorder as compared with patients with no autoimmune disorder.[6]

Different forms of autoantibodies were found in 53% of MDS patients without any clinical signs of autoimmune disorder.[18] Whether autoantibodies occur in low or high titre is not completely clear, but when they exist in patients with established autoimmune disease, not only will they occur in high titre but about 66% tend to fulfill the classification criteria of the coexisting autoimmune disease.[16]

Treatment of MDS-related SLE could be challenging because of the underlying cytopaenia and the risk of infectious complications. [19] It has been recognized from several case reports that treatment of the underlying MDS may resolve the associated SLE, and treatment of SLE with immunosuppressives has similar effect on MDS.[20,16] The selection of a particular agent may be determined by the degree of cytopaenia, which diagnosis comes first and involvement of other organs. Glucocorticoids remain the mainstay of treatment in case of leucopaenia.[21] Other immunosuppressants or immunomodulators are frequently used for their steroid sparing effect. These include hydroxychloroquine, methotrexate, cyclosporin, cyclophosphamide and mycophenolate mofetil but hematological toxicity may limit their use. The biological agents such as anti CD_{20} , anti TNF alpha and anti-IL-1 should also be considered in situation of refractory diseases or intolerance as a result of drug adverse effects.[21] The hypomethylating agents such as azacytidine and immune modulators such as thalidomide could be used especially when diagnosis of MDS comes first.

This case report has some limitations. Though our patient had SLE with refractory cytopaenia with multilineage dysplasia, there was difficulty in characterizing the specific subtype of MDS that she had because of unavailability of genetic studies in our centre.

Conclusion

Although, bone marrow involvement may be rare in SLE patients, this case report and literature review suggested that MDS may precede or complicate SLE and vice versa and therefore, to avoid misdiagnosis and delayed diagnosis any case of SLE with refractory anemia/cytopenias should be investigated extensively for MDS.

In the same vein, any case of unexplained refractory anemia/cytopenias, should be investigated for associated SLE and other autoimmune diseases.

Bone marrow biopsy and aspiration cytology should be part of the routine investigation when evaluating a patient with suspected autoimmune disease.

Acknowledgement

The authors appreciate Dr. Abubakar Saidu of Clinical Hematology unit, Internal Medicine Dept, FMC Gombe and Dr. Lawan of Histopathology Dept, FMC Gombe for their immense contribution in patient management and reporting the trephine biopsy.

Contributors

Ajibade Adenitan conceived the idea to write the case report and wrote the case report, Hakeem Olaosebikan, and Olufemi Adelowo edited the case report. Kasim Mohammed Pindiga carried out and reported the bone aspiration biopsy. All the authors approved the final version of the manuscript.

Funding and conflicting interest

Not Declared.

Consent

Obtained from the patients next of kin.

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Note

The recurrent and persistent cytopenia could not have been due to the fact that the patient is on azathioprime because:

1. Commencing the patient on disease modifyning antirheumatic drug is suppose to improve the patient's clinical condition and the patient was not on azathioprime long enough to have developed the side effect of the drug.

2. Since presentation and before the commencement of azathioprime or any other DMARDs, patient presented with and keeps representing with anaemia and leukopenia on which account she was treated with antibiotics and had reccurrent blood transfusion.

3. The bone marrow features in this patient were highly suggestive of myelodysplastic which is not a known side effect of azathioprime (to our knowledge).