Aplastic Anaemia Complicating Systemic Lupus Erythematosus (SLE) at Presentation: A Clinical Vignette and Review of Literature

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ABSTRACT

Context: Systemic lupus erythematosus (SLE) is a common disease with myriad presentation. Aplastic anaemia is occasionally associated with this disorder; however, a simultaneous diagnosis of aplastic anaemia with SLE on presentation is unusual.

Case Report: We present here, probably the first reported case of simultaneous presentation of aplastic anaemia with florid features of SLE.

Key Words: Anaemia, Aplastic; Lupus Erythematosus, Systemic; Hydroxycorticosteroids

KEY MESSAGE

- It is necessary to look out for autoimmune aetiology in every case of aplastic anaemia and to prompt a bone marrow examination in all the cases of SLE with pancytopenia.

INTRODUCTION

The haematological manifestations of systemic lupus erythematosus (SLE) commonly include anaemia(often autoimmune haemolytic anaemia), leucopaenia (usually lymphopaenia), thrombocytopaenia, recurrent arterial and venous thrombosis very often associated with anti-phospholipid antibodies (APLA). Pancytopaenia however, is relatively a rare occurrence. Pancytopaenia in SLE is more often attributed to the immune mediated peripheral destruction of the cells, rather than their underproduction in the marrow. Thus, aplastic anaemia is an extremely rare complication of SLE. Acquired aplastic anaemia remains a devastating and frustrating disease, from which a proportion of patients still die as a result of failure of support measures . Its pathogenesis remains a mystery. There are about 19 reported cases in the world literature. In most of these cases, the presentation of aplastic anaemia varied between one year prior to nine years after the diagnosis of SLE. There are however no reported cases of patients with aplastic anaemia and florid SLE at presentation. We report here, the first such case of aplastic anaemia presenting simultaneously with the classical features of SLE at onset in a 17 years old Indian female.

CASE REPORT

A 17-year-old girl presented with the complaints of progressive breathlessness and abdominal distension, which was associated with intermittent fever of three weeks duration. On examination, she had moderate pallor, icterus, right-sided moderate pleural effusion, tense ascites and bilateral pitting pedal oedema. She had tachypnoea and tachycardia at rest, with a blood pressure of 150/100 mmHg. She had facial acne and abdominal striae. Ultrasonography (USG) of the abdomen showed mild splenomegaly. The investigations revealed pancytopaenia (haemoglobin 8.76 gram %; white blood cell count 1.13 x 10^3/uL; polymorphs 50%, lymphocytes 23%, monocytes 26%, eosinophils 1%; platelets 5600/cumm), direct hyperbilirubinaemia (total bilirubin 6.4 mg/dl, direct 3.5 mg/dl), mild transaminasaemia (aspartate aminotranferase [AST] – 140 IU/L; alanine aminotransferase [ALT] – 84 IU/L) and normal alkaline phosphatase (95 IU/L) levels. She had renal failure (blood urea 110.8 mg/dl, creatinine 2.27 mg/dl). Her pleural and peritoneal effusion was found to be exudative. She had moderate proteinuria (684 mg/24 hours). Her corrected reticulocyte count was 0.82%. There was no evidence of haemolysis, as she showed normal serum haptoglobin levels and a negative Coomb's test. The bone marrow aspiration and trephine showed a hypocellular marrow with normal reticulin and few lymphoid aggregates. An initial diagnosis of aplastic anaemia was made, based on the International Aplastic Anemia Study Group criteria. She fulfilled the criteria with platelet counts < 20000/cumm and a corrected reticulocyte count of < 1%, along with a bone marrow cellularity of < 25%.

Owing to her multi-system involvement with poly-serositis, proteinuria and hepatitis, an autoimmune aetiology was considered. Her anti-nuclear antibody (ANA) was positive (1.11) and she had high titers of anti-double stranded DNA (anti-Ds DNA) of 1341 IU/l. She had mildly increased APLA antibodies (immunoglobulin G [IgG] 15.25 GPL units/ml and immunoglobulin M [IgM] 48.51 GPL units/ml), with normal anti Jo, anti-Scl-70, anti-Ro, anti-SS-A, anti-SS-B, anti-RNP and anti-Sm antibodies. Her complement levels were marginally low (C3–60.4 mg/dl and C4–18.8 mg/dl). A percutaneous renal biopsy was done, which revealed World Health Organization (WHO) class IIB Lupus nephritis – mesangioproliferative glomerulonephritis (MPGN). In view of her polyserositis, renal failure, pancytopaenia, positive ANA, and high anti Ds DNA, a diagnosis of systemic lupus erythematosus with aplastic anaemia was made. The likelihood of SLE induced pancytopaenia was considered to be unlikely, as it is usually not as severe as it was found in our patient.

She was treated with high dose Dexamethasone for four days. The patient had a dramatic improvement in her general condition after receiving steroids. She was discharged on oral Prednisolone 60 mg/day and Danazol 6 mg/day. Now, after 18 months, she is only on oral low dose Prednisolone 2.5 mg/day. Her parameters have

normalized (creatinine 0.8 mg/dl, antiDs DNA 29 IU/L, complement C3–134 mg/dl, C4–43.8 mg/dl; haemoglobin 13.2 gram %, WBC count 8.67 x 10^3/ uL, polymorphs 61% lymphocytes 31% monocytes 4% eosinophils 4%, platelets 28,20,00/cumm). She is in complete remission and on regular follow up.

DISCUSSION

The haematological manifestations of SLE typically include anaemia of chronic disease, lymphopaenia, immune thrombocytopaenic purpura, autoimmune haemolytic anaemia. These features may occur in up to 59% of the patients. However, the occurrence of pancytopaenia, myelofibrosis and aplastic anaemia is an extremely rare complication of SLE. There are 19 such reported cases in the world literature. Among the 20 reported cases, including ours, which have been reviewed here [Table/Fig-1], a female preponderance was found, with more than 80% of the patients being females and the age group varied between five months to 74 years, with mean age of 27.4 years. In most of the cases, aplastic anaemia either preceded the diagnosis of SLE, or developed later during the course of the illness. Chute et al.[1] described two cases, one of a 35 year old female and another, a 33-year old Hispanic male, who presented with aplastic anaemia as the sole presentation and after a period of 3 and 12 months respectively, developed the features of SLE. In the remaining cases, the time of the onset of aplastic anaemia varied between 1 yr before the diagnosis of SLE, up to 9 years after the diagnosis. To the best of our knowledge, ours is the first case which describes the occurrence of aplastic anaemia at presentation with the classical symptoms of SLE.

The therapy for immune-mediated dysfunction commonly includes pulse glucocorticoids alone or in combination with pulse cyclophosphamide. However, for those patients with an aggressive, life threatening or refractory disease, experimental therapies such as plasmapheresis or intravenous immunoglobulin may be used as adjuncts for their management. All the reported patients showed a complete response to the immunosuppressants. Eight patients showed a good response to the high dose steroids and the remaining patients were treated with cyclophosphamide or cyclosporine or plasmapheresis. Of the eight patients who were treated with steroids, only three of them had received courses of steroids prior to the diagnosis of aplastic anaemia. All the other patients were on regular steroids when they developed aplastic anaemia. In this group, two patients succumbed to opportunistic infections. Wolach et al. [2] reported the first case of a baby who was born to an SLE mother. The infant presented with severe anaemia and with a circumscribed, reticular, macular rash on the face and neck at five months of age. A skin lesion biopsy revealed epidermic hyperkeratosis, hydropic degeneration of the basal layer, and the deposition of the immunoglobulins and the granular C1q at the dermoepidermal junction. Ro/SS-A antibodies were present in the infant, who showed good response to the steroids initially. The infant succumbed to infections at the age of 16 months. Pavithran et al. [3] reported the other case of a 32-year-old female who was initially diagnosed to have immune thrombocytopenic purpura (ITP) and was managed on this basis for 18 months. She later developed progressive pancytopaenia, polyarthritis and extensive rashes, which on further investigation, was proved to be SLE with aplastic anaemia. She also died due to fulminant infections.

The aplastic anaemia in SLE responds well to immunosuppressive therapy and has a relatively better prognosis, as compared to other causes of aplastic anaemia. The aplastic anaemia in SLE is likely to be immune mediated, considering its good response to immunosuppressive therapy.

The hypothesis of bone marrow aplasia, it being autoimmune in nature, is supported experimentally by some of the studies. Brooks et al. [4] demonstrated that the IgG complement-dependent antibody which was obtained from the patient's disease-phase

No	Year	First author	Age	Sex	Treatment prior to onset of aplastic anemia	Aplasia Onset	Treatment after onset of aplastic anemia
1	1979	Fitchen JJ [8]	36	F	Prednisolone, Methyl prednisolone.	After 4 months	Plasmapheresis (6 cycles).
2	1981	Abdou NI [9]	20	F	Prednisolone, HCQS, zathioprine.	After 4 years	Plasmapheresis (4 cycles).
3	1982	Walport MJ [10]	22	F	Prednisolone, Azathioprine.	After 3 years	Cyclophosphamide, IVIG.
4	1984	Brooks BJ Jr [4]	17	F	Prednisolone.	After 7 months	Plasmapheresis (4 cycles), IVIG.
5	1984	Stricker RB [11]	19	F	Prednisolone, Phenytoin.	After 9 years	Oxymethalone.
6	1984	Stricker RB [11]	25	F	Prednisone, Phenytoin, Chlorambucil.	After 5 years	Oxymethalone.
7	1988	Winkler A [12]	48	F	Methyl prednisolone, Cyclophosphamide.	After 4 months	Cyclophosphamide.
8	1989	Bailey FA [13]	17	F	Prednisolone, Azathioprine.	After 1 year	Plasmapheresis (6 cycles).
9	1989	Fischer [14]	74	F	NA	NA	Cyclosporine A.
10	1991	Roffe C [5]	31	F	Prednisolone.	NA	Cyclophosphamide.
11	1991	Sumimoto S [7]	6	F	Methyl prednisolone, IVIG.	After 3 months	Methyl prednisolone.
12	1993	Wolach B [2]	5 mo	F	Prednisolone.	5 months	Prednisolone.
13	1995	Marques JA [6]	41	F	Prednisolone.	After 5 years	Methyl prednisolone, IVIG, Plasmapheresis.
14	1996	Chute JP [1]	31	M	–	After 1 year	Prednisolone.
15	1996	Chute JP [1]	35	F	–	After 3 months	Prednisolone.
16	1998	Tagoe C [15]	26	M	–	After 6 months	Prednisolone.
17	1998	Tagoe C [15]	24	F	Prednisolone.	Before 6 months	Methyl prednisolone.
18	2002	Singh NP [16]	22	F	Steroids.	After 7 months	Cyclosporine.
19	2002	Pavithran K [3]	32	F	Steroids.	After 14 months	Methyl prednisolone.
20	2010	Our case	16	F	–	At presentation	Dexamethasone, Prednisolone, Danazol.

[Table/Fig-1]: M – Male; F – Female; mo – months; HCQS – Hydroxychloroquine sulphate; IVIG – Intravenous Immunoglobulin; NA – Not available

serum but not from the remission-phase serum, suppressed the growth of the granulocyte-macrophage progenitor cells from the bone marrow of normal donors in vitro. Therapy with plasmapheresis and immunosuppression resulted in a lasting remission in their patient. Roffe et al. [5] postulated that the marrow aplasia might have been an autoimmune cellular process, as they demonstrated that bone marrow cultures showed the inhibition of erythropoiesis when they were incubated with acute and remission serum. But either serum did not affect the myeloid colony growth. Marques et al. [6] also did similar bone marrow culture studies, but they demonstrated a marked suppression of both haematopoiesis and myelopoiesis when various titers of the patient's plasma were included in the culture media. The control plasma produced no inhibition. Sumimoto et al. [7] demonstrated increased numbers of CD8 cells in the marrow and suggested that the aplastic anaemia was caused due to a cell mediated process with the CD 8 cell mediated suppression of the bone marrow.

In our case, we did not do any in-vitro studies to prove the suppression of haematopoiesis on the stem cell or progenitor cell level due to the lack of availability of such tests locally. This would be helpful in definitively proving aplasia in this patient; however, we believe that the occurrence of the features which are classically diagnostic of aplastic anaemia with SLE in a patient who was absolutely asymptomatic three weeks prior, is significant enough to prove the association between SLE and aplastic anaemia.

CONCLUSION

We present a case of SLE with aplastic anaemia at presentation and this, to the best of our knowledge, is the first case which has been reported in the world literature. The diagnosis was not difficult due to the multi-system involvement, but it clearly suggests a need to look out for the autoimmune aetiology in every case of aplastic anaemia and the necessity to do a bone marrow examination in all cases of SLE with pancytopaenia, especially because aplastic anaemia in SLE has a higher chance of going into complete remission with properly tailored immunosuppressant therapy.

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