

Multisystem Failure Due to Three Coexisting Autoimmune Diseases

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Abstract

Systemic lupus erythematosus (SLE) is a potentially fatal, autoimmune disease, which can affect different organs and can present with protean clinical manifestations. It may be associated with many other autoimmune conditions and two rare such conditions are myelofibrosis and acquired haemophilia. Autoimmune myelofibrosis is a bone marrow disorder characterized by pancytopenia, which can occur in conjunction with the presenting features, or an exacerbation of previously established SLE. Acquired haemophilia is another rare disorder of haemostasis, which can be life threatening without prompt and appropriate treatment. The management of these different conditions in itself poses a difficult problem but when the three conditions present simultaneously in the same individual, the accurate diagnosis and indeed the appropriate management becomes extremely challenging. This report describes a young woman who presented with pancytopenia secondary to myelofibrosis and panserositis with no identifiable precipitating factors. Her condition deteriorated rapidly and she required intensive care support for respiratory failure and renal impairment. A presumed diagnosis of SLE was considered and treatment was initiated which improved and stabilised her condition. However, she developed bleeding complications from acquired haemophilia which required further specialist intervention. Multidisciplinary management of the patient helped in the resolution of the complications and stabilisation of her autoimmune conditions. This report should make physicians aware of the rare presentations of SLE and its complex management.

Key words: haemophilia, systemic lupus erythematosus, myelofibrosis

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Introduction

Systemic lupus erythematosus (SLE) is considered the archetypal systemic autoimmune disease, clinically characterized by multisystem involvement and varied serologic abnormalities. No two patients with SLE present or have disease that evolves in exactly the same way and the clinical picture of SLE is dictated by the relative contributions of the organs affected by the characteristic autoantibodies. For this reason, diagnostic criteria has been created by the American College of Rheumatology (ACR), which includes 11 categories, wherefrom four or more must be present to diagnose SLE (1). Haematological disorders form a part of

these criteria and include thrombocytopenia, leukopenia and lymphopenia, and hemolytic anemia (1). Beyan et al carried out a study of haematological abnormalities in SLE patients and found that most of the patients had anemia at the time of presentation due to various etiologies (2). Anemia of chronic disease (46%) was the most common picture, with another 28% having hemolytic anemia. Leukopenia and lymphopenia were noted in 57% and 82% of the patients, respectively, while thrombocytopenia was seen in 40% of the cases. Although single cytopenias may occur alone or in combination at the onset of SLE, pancytopenia is not a common feature and is usually secondary to immunosuppressive treatment, like azathioprine and rarely, myelofibrosis. The latter is a disorder where there is reduced hemopoiesis.

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isis because of fibrotic transformation of the bone marrow. It usually arises as a clonal disorder but can also be associated with SLE where the autoantibodies attack the marrow architecture, in which instance it is then termed autoimmune myelofibrosis (3). Autoimmune myelofibrosis presents as pancytopenia and usually resolves with the treatment of SLE though blood transfusion support may be necessary until its resolution.

SLE is also a commonly recognized prothrombotic condition especially when it is associated with the antiphospholipid syndrome. However, bleeding is a rare complication in individuals with this condition and can arise due to antibodies against the clotting factors especially factor VIII, when it is called acquired haemophilia (4). These patients can present with severe mucosal haemorrhage and internal bleeding, which can occasionally be fatal. Early recognition and treatment is therefore essential to prevent the catastrophic bleeds in these patients.

The management of SLE involves immunosuppressive treatment including steroids, cytotoxic drugs, monoclonal antibody therapy, rituximab or combinations thereof which can successfully eradicate the autoantibodies against the bone marrow and the clotting protein.

Case Presentation

A 40-year-old woman initially presented to a district hospital with acute abdominal pain and lethargy. She did not have any past medical or surgical history of note and was not on any medications. There was also no family history of any significant illnesses. Physical examination was normal at presentation. Blood investigations revealed abnormal liver function tests [serum bilirubin -18 mmol/L (normal range: 2-17 mmol/L); alkaline phosphatase -415 units, (normal range: 35-125 units); gamma glutaryl transferase -225 units (normal range <35 units)]. Her other biochemical and haematological investigations were normal. Hepatitis virology screen, upper gastrointestinal endoscopy and ultrasound abdomen were undertaken, all of which revealed no abnormalities. Her symptoms were resolved and she was discharged with a follow-up plan.

However, she re-presented three weeks later with asthenia, fever, dyspnoea and abdominal distension. On clinical examination, she was found to have bilateral pitting oedema, pleural effusion and ascites. Blood tests at this time showed a pancytopenic picture (hemoglobin [Hb] -10.6 g/dL; neutrophils $-0.0 \times 10^9/L$; platelets $-25 \times 10^9/L$). Her liver functions tests were similar to the previous results except for a very low serum albumin -17 g/dL (normal range 35-45 g/dL). The blood urea was raised at 19 mmol/L (normal range: 2.5-7.0 mmol/L) and creatinine was 130 $\mu\text{mol/L}$ (normal range: 50-130 $\mu\text{mol/L}$). Her urine microscopy did not show any leukocytes or organisms but her 24 hour urine protein excretion was increased at 0.42 gm/day. She was referred to our university hospital for further management.

Further investigations arranged at our hospital included a

direct antiglobulin (Coombs) test which was strongly positive, suggesting a possible autoimmune process. Reticulocyte count, serum haptoglobins (3.7 mg/dL; normal range -0.5 to 2.0 mg/dL), and lactate dehydrogenase levels were all normal excluding haemolytic anemia. Serum B12 and red cell folate concentrations were within normal limits. Blood cultures grew *Staphylococcus epidermis*. Repeat virology tests for EBV, CMV, HIV and other hepatitis viruses were negative. Autoimmune screen was normal apart from very high anti-nuclear antibodies of 1:320 with a speckled pattern (negative anti-mitochondrial antibody, anti-smooth muscle antibody, anti-neutrophil cytoplasmic antibodies and anti-extractable nuclear antibodies). An anti-double stranded antibody (dsDNA) was also negative. Complement levels were slightly reduced (C4 -0.16 g/dL; normal range -0.18 to 0.58 g/L, C3 -0.71 g/L; normal range -0.70 to 1.70 g/L).

A repeat abdominal ultrasound revealed hepatomegaly (with normal echo texture) and ascites. The kidneys, spleen and portal vein were normal. Computerised tomography scan showed bilateral pleural effusion, ascites but no evidence of any lymph node enlargement. An echocardiogram showed minimal pericardial effusion with normal cardiac function. Pleural, pericardial or ascitic fluid aspiration was not undertaken to avoid any infectious contamination during severe neutropenia. However, a bone marrow aspirate was performed to identify the cause of pancytopenia. This revealed a dry tap, but the trephine biopsy was hypercellular with increased megakaryocytes (corresponding with the areas of fibrosis) and reticulin ((Figure 1 demonstrates the hypercellular marrow and Fig. 2 demonstrates the grade 3 fibrosis on special staining) consistent with a histopathological diagnosis of acute myelofibrosis. A liver biopsy demonstrated focal fatty infiltration. Her condition soon deteriorated with worsening breathlessness and renal impairment (blood urea -22.6 mmol/L; serum creatinine -204 $\mu\text{mol/L}$).

She was treated with intravenous antibiotics tazocin, teicoplanin and granulocyte colony stimulating factor (GCSF). GCSF failed to improve the neutrophil count. Although, the patient's dsDNA was negative, the presence of four clinical parameters including i) renal impairment, ii) serositis (pleural and pericardial effusions and ascites), iii) leucopenia and thrombocytopenia, and iv) positive antinuclear antibody satisfied the ACR criteria for the diagnosis of systemic lupus erythematosus (SLE).

A retrospective history revealed Raynaud's disease, alopecia, second trimester miscarriage, and significant vaginal bleeding during two of three previous pregnancies. Daily intravenous methylprednisolone 500 mg for 5 days was administered. She was also given maintenance oral steroids (prednisolone 60 mg OD). Her fluid overload, progressive renal and respiratory failure was managed by haemodialysis and continuous positive airway pressure in the intensive care unit. She improved well with treatment.

Almost four weeks after the initial presentation, she developed a left upper arm and right buttock swelling. A possible diagnosis of deep vein thrombosis due to antiphosphol-

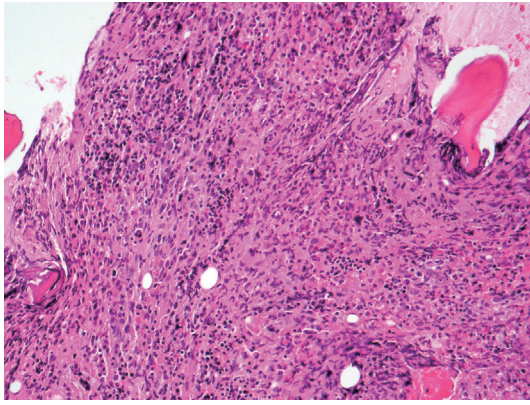


Figure 1. High power image of the bone marrow showing hypercellularity.

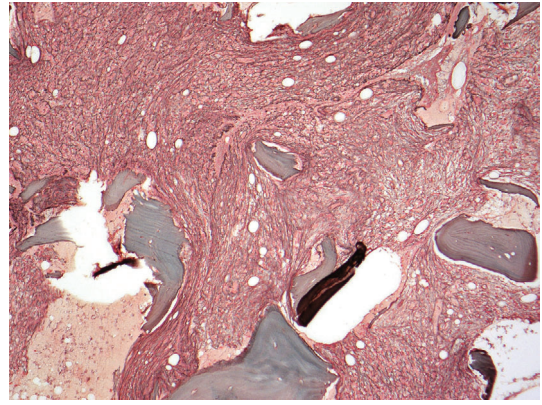


Figure 2. Reticulin staining of the bone marrow showing increased fibrosis.

lipid syndrome secondary to SLE was considered. Surprisingly, a Doppler ultrasound of the arm revealed an intramuscular haematoma in the place of an upper limb deep vein thrombosis. Clotting investigations were undertaken at this point which demonstrated a prolonged activated partial thromboplastin time (APTT) of 65.8 seconds (normal range -23-35 seconds) while the prothrombin time (PT) was normal. Mixing studies revealed a strongly positive lupus anticoagulant. However, it also demonstrated low factor VIII levels of 15% (normal greater than 50%) and strong inhibitors to factor VIII. The Bethesda assay, confirmatory test for acquired haemophilia, showed an increased titre of 10 units. The combination of a strongly positive lupus anticoagulant and the presence of antibodies to a coagulant protein posed diagnostic dilemma in the laboratory. However, a clinical picture of bleeding rather than thrombosis favoured the diagnosis of acquired haemophilia rather than antiphospholipid syndrome wherein thrombosis is usually the predominant picture. Further evidence against antiphospholipid syndrome was provided by the laboratory tests. In antiphospholipid syndrome, the antibodies present tend to inhibit more than one coagulation factor, but the test results of the present patient only showed reduced factor VIII levels and not others (factor IX -97%, factor XI -68%, factor XII -69%). Anticardiolipin antibodies were within normal range (IgG -3 GPL and IgM -3 MPL; normal range for both -less than 10 GPL or MPL) and the Dilute Russel Viper Venom test ratio (DRVVT) was also normal (0.90; normal is less than 1.0). This diagnostic decision was supported by the resolution of her haematoma with treatment using recombinant activated factor VIIa (Novoseven) with no thrombo-embolic complications. Immunosuppression with cyclophosphamide 50 mg daily was also initiated and doses were titrated up. She also received a further course of methylprednisolone for 3 days. After a hospital stay of twelve weeks, she was discharged with stable blood count, normal renal and liver function tests (Hb -10.3 g/dL; neutrophils - $8.7 \times 10^9/L$; plts - $361 \times 10^9/L$; APTT -40 secs; FVIII -102%). A summary of the blood results during the different clinical presentations corresponding to the diagnoses of the three autoimmune conditions are

given in Table 1 and Fig. 3.

At present, almost four years later, she is maintained on mycophenolate mofetil and prednisolone (5 mg daily) as immunosuppressive agents. Her symptoms are now of lethargy and occasional bruising. Although she has not managed to resume a full time job, she does volunteer work in after-school art classes. Her clotting screen is now normal and she is lupus anticoagulant and anti-cardiolipin antibody negative.

Discussion

SLE is a clinically heterogeneous disease demonstrated by the unusual presentation in this report. Because of the varied presentation, diagnostic criteria have been developed for this condition, which include clinical manifestations, alongside laboratory results (1). These criteria take into consideration several systemic manifestations including haematological abnormalities. Pancytopenia is rare in SLE but can be associated with myelofibrosis (5). Myelofibrosis can be classified as primary (clonal disorder of the bone marrow) when it is called idiopathic myelofibrosis and secondary, when it arises due to other pathological conditions (6). Secondary myelofibrosis is often found in association with malignancy and chronic infections like HIV and tuberculosis (7). It has also rarely been described with SLE and other autoimmune disorders, when it may be called autoimmune myelofibrosis (7, 8).

Pullarkat et al have argued that autoimmune myelofibrosis is a separate clinicopathologic syndrome, characterised by cytopenias, bone marrow lymphocyte infiltrate and grade 3 or 4 reticulin fibrosis; absence of atypical bone marrow cells; absent or minimal spleen and presence of auto antibodies (9). In this study, 76% of patients had increased reticulin deposition in the bone marrow as was noted in the present patient. Pereira et al examined 21 bone marrow trephines in patients with SLE and peripheral cytopenias and established that in almost half of the patients, global hypocellularity and granulocytic hypoplasia were present (8). In this context, it should be noted that hypercellularity was

Table 1. Laboratory Data Corresponding to the Clinical Presentation of the Patient

Days	- 21	01	03	09	28	50	80	4yrs
Clinical stage	Previous hospital	Admission	ITU	Post ITU	Bleed left upper arm	After VIIa treatment	Outpatient 3 months	Outpatient 4 years
Hemoglobin (g/dL)	13.6	10.6	6.8	8.8	6.0	10.1	13.5	14.2
WCC ($\times 10^9/L$)	4.5	1.2	0.8	4.8	10	5.5	8.2	9.5
Plt ($\times 10^9/L$)	215	25	21	49	196	415	319	290
Urea (mmol/L)	6.1	19	24.6	9.5	16.4	6.9	6.0	6.4
Creatinine ($\mu\text{mol/L}$)	68	130	204	75	183	61	76	67
Bilirubin ($\mu\text{mol/L}$)	18	19	16	22	21	18	7	8
ALT (U/L)	24	22	08	18	22	12	28	11
Alkaline Phosphatase (U/L)	415	405	223	327	187	148	97	68
Albumin (g/L)	29	17	22	25	29	28	38	43
PT (in seconds)	N/A	13.0	13.0	13.3	13.4	13.2	11.8	11.6
APTT (in seconds)	N/A	35.9	35.4	31.4	65.8	54.0	39.7	28.9

Abbreviations: PT- prothrombin time; APTT –activated partial thromboplastin time; ALT – alanine aminotransferase; ITU – intensive care unit; WCC- white cell count; Plt – platelet count, N/A – not available.

found in the examination of the bone marrow of our patient, which differs from that previously described in the literature.

The main treatment of SLE-associated autoimmune myelofibrosis is corticosteroids, which has demonstrated good clinical effects with resolution of the bone marrow fibrosis (7). In the present patient, the latter was not confirmed by a further trephine, however peripheral blood samples were correlated with a positive response in the bone marrow. Interestingly, fibrosis which is primarily reticulin based often responds to steroids. In contrast ‘collagen fibrosis’, occurring in idiopathic myelofibrosis, has been shown to be more refractory to steroid therapy (10).

SLE is also well known to be a prothrombotic condition, when it is associated with antiphospholipid syndrome. But, very rarely it can present with bleeding manifestations which can arise due to a rare condition, acquired haemophilia [AH] (11). The diagnosis of a haemostatic disturbance associated with SLE can be difficult as exemplified by the present case. An abnormality in the clotting mechanism is usually detected when there is a prolongation of the clotting

test including PT or APTT. The APTT is more often abnormal in SLE and can be due to lupus anticoagulant, which can present as a thrombotic disorder. An abnormal clotting result once noted is further characterized by the mixing studies where plasma from an individual with normal amount of clotting factors is mixed with that of the patient with the abnormal result (12). If the APTT is corrected, it suggests a clotting factor deficiency and if not, an inhibitor to the factor is likely. The latter can be a lupus anticoagulant or an inhibitor to the clotting factor, commonly factor VIII. The differentiation of these can be difficult. If only one clotting factor is reduced by the inhibitor, it suggests against lupus anticoagulant where antibodies can affect the laboratory estimation of more than one factor. Another important differentiating feature is the clinical information which suggests lupus anticoagulant, if there is a thrombotic history or presentation and AH, if there are bleeding concerns in the patient.

AH is caused by auto-antibodies to coagulation factor VIII resulting in a depletion of circulating levels of factor

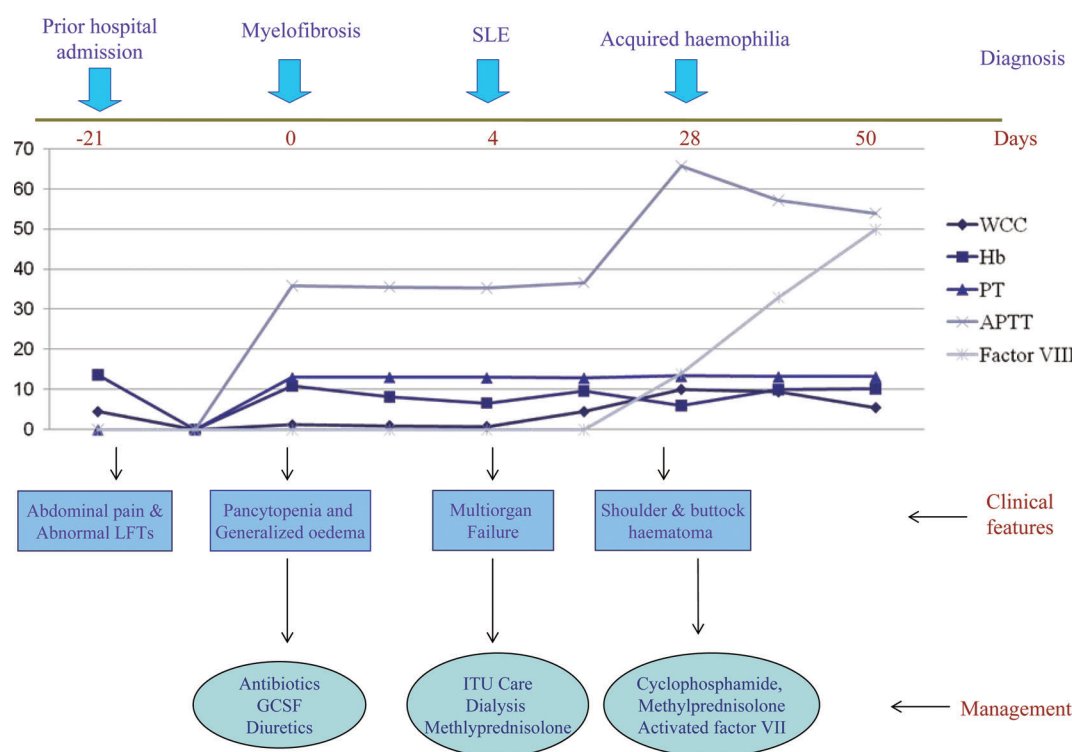


Figure 3. Figure detailing the clinical course of the patient. The clinical course in days is correlated with the blood results, diagnoses and management. Abbreviations: Hb: hemoglobin, WCC: white cell count, PT: prothrombin time, APTT: activated partial thromboplastin time

VIII protein (9). Inhibition of Factor VIII, which functions as a cofactor for Factor IXa in the enzymatic activation of Factor X, leads to a reduction in the generation of thrombin on the surface of activated platelets (13). AH is a rare disorder with an estimated incidence of 1.48 cases per million a year in the UK (14). Case series have shown that underlying diseases are identifiable in up to 50% of cases (15). These include autoimmune diseases including rheumatoid arthritis (7.9%), SLE (5.7%), malignancy (6.7%), pregnancy (7.3%) and drug reactions (6%) (16).

Bleeding, associated with AH usually occurs in the mucosal areas as ecchymoses but can also cause intramuscular haematoma, as in this case. The UK study suggested that fatal bleeding can occur in 9.1% of all cases (14) and other studies have suggested severe life-threatening bleeds occur in more than 85% of cases (4). Treatment of bleeding in AH has been evaluated by moderately sized clinical trials and efficacy has been demonstrated for porcine factor VIII (17), recombinant factor VIIa (rFVIIa) (18) and factor eight inhibitor bypassing activity (19). In this case, bleeding due to AH was controlled with rFVIIa. The exact mode of action of this agent is yet to be elucidated, but it is believed to generate local thrombin formation by enhancing the tissue factor/ FVIIa action at the site of injury, which then acti-

vates factors X and IX (20). A cell-based model of haemostasis has indicated that high dose rFVIIa binds to activated platelets with a low affinity and activates factor X independently of tissue factor (21).

In order to eradicate the factor VIII antibodies, it is also common practice to commence a form of immunosuppressive therapy. However, spontaneous remission has been observed with AH related to pregnancy and post-partum periods (22). Our patient received cyclophosphamide initially, which was changed to mycophenolate mofetil for immunosuppression. Throughout the initial episode and later, she was also prescribed corticosteroids, which has been tapered over time and maintained on a smaller dose, on which her symptoms are minimal.

In conclusion, this report is a very rare presentation of autoimmune myelofibrosis, autoimmune haemophilia and multi-system failure in the context of SLE, which has been managed successfully. This should encourage physicians managing patients with SLE to consider the possibility of coexisting autoimmune conditions when rare complications arise. The successful management of such patients should involve a multidisciplinary approach which may also help in improving the understanding of the pathophysiology of these associated autoimmune conditions.

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