

Significance of autoimmune haemolytic anaemia and immune thrombocytopenia (Evans' Syndrome) in Systemic Lupus Erythematosus

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Abstract

Patients with systemic lupus erythematosus (SLE) have an extremely variable prognosis and mortality. The purpose of this report is to highlight the importance of looking for lupus parameters in patients with autoimmune haemolytic anaemia (AIHA) and/or immune thrombocytopenia (ITP) as this represents a subgroup of systemic lupus erythematosus (SLE) patients with a fairly good prognosis. We report a case of an 8-year-old Malay boy who was admitted to hospital with fever and gum bleeding. Physical examination revealed a malar rash, oral ulcers, petechial haemorrhages and bruises over the limbs, generalised lymphadenopathy and hepatosplenomegaly. Laboratory investigations confirmed the diagnosis of SLE. The patient's serum showing the presence of antinuclear factor, antiphospholipid antibodies and a biological false-positive test for syphilis. Immunological and haematological parameters were in keeping with combined AIHA and ITP (Evans' syndrome). No organ involvement was present and the patient responded well to corticosteroid therapy. This case demonstrates the importance of making an early diagnosis of SLE with haematological complications, in order to ensure full benefit of therapy and emphasises the good prognosis expected in this subgroup of SLE patients.

Key words: Systemic Lupus Erythematosus, haemolytic anaemia, thrombocytopenic purpura, Evans' syndrome, antiphospholipid antibodies.

INTRODUCTION

Haematological abnormalities are frequently encountered in patients with Systemic Lupus Erythematosus (SLE) and are part of the American Rheumatoid Association criteria for diagnosis of the disease. Acquired autoimmune haemolytic anaemia and/or thrombocytopenic purpura may be presenting signs of SLE and may predate the appearance of diagnosable SLE by many years. These haemocytopenias may also occur in patients with SLE during the course of their illness. In 1951, Evans *et al* and later Alger *et al* suggested that these haematological manifestations could indicate two related subsets of SLE.

We report here a patient with SLE whose main presenting symptoms were autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenia and discuss the significance of these haematological abnormalities in the course of the disease.

CASE REPORT

An 8-year-old Malay boy presented with a four-day history of moderate grade fever associated with upper respiratory tract infection and gum

bleeding. The child was initially treated by two general practitioners symptomatically and was given antibiotics, (Bacampicillin later changed to Amoxycillin) and cough mixture. As there was no improvement and the gum bleeding worsened, the child was brought to the Paediatric Institute, General Hospital, Kuala Lumpur.

There was no past history of easy bruising or excessive bleeding after tooth extraction and no history of bleeding from other sites such as haematemesis, haematuria or malaena. There was no significant family history of bleeding disorder. No history of loss of appetite, joint pains, bone pain or weight loss was obtained. There was no history of hair loss or urinary symptoms.

Physical examination revealed a pale, febrile, well built child. There was moderate bleeding from the gums with oral ulcers over the hard palate and on the right side of the buccal mucosa. There was no jaundice and no fundal haemorrhages. The child's blood pressure was 110/70 mm Hg. Hess test was negative. Haemorrhages and bruises were present over the upper and lower limbs. A maculo-papular, malar rash was noted over the face. There was generalised lymph node enlargement involving

the cervical, inguinal and axillary lymph nodes. The lungs were clinically clear and the cardiovascular system did not reveal any abnormality. The liver was enlarged 3cm from the right costal margin and the spleen was palpable 4 cm below the left.

An initial clinical diagnosis of dengue haemorrhagic fever was made with a differential diagnosis of acute leukaemia/lymphoma and Systemic Lupus Erythematosus. The full blood picture on admission showed a haemoglobin level of 7.4% g/dl with a reticulocyte response of 4.2%. Autoagglutination was present. The total white cell count was $4.2 \times 10^9/L$ with a differential count of polymorphs 53%, lymphocytes 35%, monocytes 9%, eosinophils 0% and atypical lymphocytes 2%. There was moderate thrombocytopenia ($82 \times 10^9/L$). The direct antiglobulin test was positive for IgG and complement. The indirect antiglobulin test was also positive. Antibody studies revealed a pan-agglutinating auto-IgG antibody and a cold auto anti-I antibody of low titer. A diagnosis of autoimmune haemolytic anaemia with thrombocytopenia (Evans' syndrome) was made. The ESR on admission was 160mm/hr. Bone marrow examination showed a reactive marrow aspirate with active erythropoiesis and numerous megakaryocytes, with many 'young' megakaryocytes present - findings in keeping with auto-immune haemolytic anaemia with immune thrombocytopenia.

Tests for platelet antibodies were carried out and these revealed the presence of IgG on platelets by immunofluorescence technique. Coagulation studies revealed a prolonged prothrombin time (patient 20.9 sec; control 12 sec) and partial prothromboplastin time (patient 71 sec; control 35 sec) with increased fibrinogen. The screen for lupus anticoagulant was positive. Antinuclear factor was positive. Tests for rheumatoid factor and anti-DNA were negative. Tests for LE cells were negative on 3 occasions. The VDRL test was positive (1 : 2 dilution). TPHA was negative. The level of complement components C3 and C4 were measured and both were low.

The patient had one episode of haematuria and albuminuria while in the ward. The urine was subsequently clear. The renal profile remained normal. The patient also had one episode of left sided focal fit while in the ward. CT scan did not show any evidence of a bleed or infarct. A final diagnosis of autoimmune haemolytic anaemia with immune thrombocytopenia (Evans' syndrome) in SLE

was established.

The patient was immediately started on prednisolone. There was tremendous improvement. The temperature settled and gum bleeding stopped. As the patient's haemoglobin level was only 6.6 g/dl, he was transfused 2 units of packed red cells. The haemoglobin level improved from 6.6 g/dl to 10.5 g/dl 2 days later. The total white cell count, platelet count and ESR also improved. Patient was discharged 10 days after starting therapy with a haemoglobin level of 11.6 g/dl, total white count of $9.0 \times 10^9/L$ and a platelet count of $224 \times 10^9/L$.

DISCUSSION

Haematological abnormalities are frequently encountered in patients with SLE. Anaemia is the most common abnormality, being reported in 57% to 78% of patients with this disease.¹ The causes of anaemia are multiple and may be of immune or non immune pathogenesis. Contrary to popular belief, the most common cause of anaemia in this disease is not 'auto-immune' but rather the anaemia of chronic disease.¹

Autoimmune haemolytic anaemia (AIHA) in SLE has been quoted to occur in 3-40 % of patients sometime during the course of the disease.^{2,3} This may be the sole presenting feature of SLE and has been reported to antedate the appearance of other diagnostic features by many years. It has been suggested that so-called idiopathic auto-immune haemolytic anaemia may be a form fruste of SLE.¹ In as many as 20% of patients with idiopathic autoimmune haemolytic anaemia a diagnosis of SLE is established at some time.³

The direct antiglobulin test is the standard clinical assay used to establish a diagnosis of immune haemolytic anaemia. Although this test is positive in 18-65% of patients with SLE, a positive test in itself does not establish that an anaemia is caused solely or predominantly by anti-erythrocyte antibodies.³ A positive direct antiglobulin test implies one of three patterns of protein deposition on the erythrocytic surface: (1) immunoglobulin (Ig) alone, (2) Ig and complement (usually C3 or C4), or (3) complement alone. In patients with SLE with clinical haemolysis, the antiglobulin test is usually positive for both IgG and C3 or for C3 alone. Patients with SLE without clinical haemolysis frequently have positive antiglobulin tests for C3d only. A positive antiglobulin test for IgG alone is believed to be so rare in SLE that it is suggestive of a non-lupus erythematosus cause

for the autoimmune haemolytic anaemia.² However, the converse is not true because the majority of patients with idiopathic autoimmune haemolytic anaemia are positive for IgG and complement or complement alone. All four subclasses of IgG are generally present on the cells and both IgM and IgA are sometimes present as well.³ Thrombocytopenia is a well recognised complication of SLE. In 1960, Rabwowitz and Domestick emphasized the close association between ITP and SLE and suggested that ITP is often a prodrome of this syndrome.

Episodic thrombocytopenia occurs frequently in active SLE and persists in 20% of patients.³ Platelet destruction is probably mediated either by auto-antibodies against platelet membrane associated antigens or by attachment of immune complexes to the platelet surface resulting in enhanced uptake by the reticuloendothelial system.⁴ Several studies have demonstrated increased platelet-associated IgG both in thrombocytopenic patients and non-thrombocytopenic patients with SLE.

A more recent study shows that a high proportion of SLE patients who have autoimmune haemolytic anaemia and thrombocytopenic purpura either simultaneously or sequentially have antiphospholipid antibodies.⁵ Antibodies to cardiolipin, reagin antibodies responsible for a biological false-positive test for syphilis and lupus anticoagulant are normally grouped as antiphospholipid antibodies. Their presence in patients with SLE and other autoimmune diseases have been associated with thrombosis, thrombocytopenia and recurrent foetal losses. One of the proposed mechanisms through which antiphospholipids might be responsible for this is their reaction with phospholipids in the endothelial cell membranes blocking thereby arachidonic acid release and resulting in reduced prostacyclin production. Decreased prostacyclin levels would cause increased platelet aggregation and thrombosis.⁶ Antiphospholipids could also cause erythrocyte disruption. This would explain how thrombosis, haemolytic anaemia and thrombocytopenia could exist as part of the antiphospholipid antibody syndrome. It has been postulated that infection could act as a trigger and stimulate the production of antiphospholipid antibodies.⁵

Patients with SLE have an extremely variable prognosis and mortality. In 1975, Fries and Helman claimed that patients with systemic lupus erythematosus may be grouped in different subsets considering their clinical or laboratory manifestations. Since then several attempts have

been made to distinguish groups of patients with mild disease and better prognosis from those having a progressive accelerated disease. Many studies support the concept that SLE patients with haematological manifestations represent a subset with slow disease progression and that the benign course of the disease is not worsened by splenectomy.⁷ Corticosteroids is the first modality of treatment for patients with SLE-related immune haemocytopenias and this produces good response in approximately 75% of patients.⁷ The other treatment modalities are splenectomy and the use of non-steroidal immunosuppressive drugs such as azathioprine and cyclophosphamide. The splenectomy rate has been reported to be low in this subset of patients with haematological manifestations.⁷

In our case, the patient's main presenting symptoms were due to the autoimmune haemolytic anaemia and immune thrombocytopenia. The patient also revealed the presence of lupus anticoagulant and a biological false-positive test for syphilis. This is in keeping with a previous study which showed that a high proportion of SLE patients who develop both autoimmune haemolytic anaemia and thrombocytopenic purpura during their course have antiphospholipid antibodies.⁵ Many reports indicate that the presence of these antibodies is a useful marker for patients at risk for the development of thromboembolic complications and for cerebral manifestation of SLE.⁸ Our patient would probably require long term regular close monitoring.

It is also interesting to note the history of upper respiratory tract infection in our patient. A literature search reveals 5 patients who had respiratory infection (streptococcal pharyngitis and pneumococcal pneumonia) prior to or coincidental with the development of autoimmune haemolytic anaemia, thrombocytopenia and antiphospholipid antibodies.⁵

As in previous reports, our patient responded well to prednisolone therapy. His fever subsided and his gum bleeding stopped two days after the commencement of therapy. Full blood counts improved after two days. The patient has been well since, and is currently on low dose prednisolone.

This case illustrates the need to look for lupus parameters in patients which autoimmune haemolytic anaemia and immune thrombocytopenia in order to establish an early diagnosis and initiate prompt therapy. It is also important to identify subgroups of SLE patients with different clinical and/or serological

manifestations as patients with SLE can have an extremely variable prognosis and mortality. More attempts are required to confirm previous findings and to recognize new subgroups.

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