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Pathophysiology and Clinical assessment of anemia in Systemic lupus erythematous .

Medicine

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RAJENDRA.V. BHAGWAT M.D.Medicine, Government Medical College, Miraj & Padmabhushan Vasantdada Patil Govt. Hospital, Sangli. Maharashtra, INDIA.

NANDKUMAR.N. PATIL DNB Medicine, Government Medical College, Miraj & Padmabhushan Vasantdada Patil Govt. Hospital, Sangli. Maharashtra, INDIA.

ABSTRACT

Hematological abnormalities are very common in systemic lupus erythematosus.

Anemia is most common hematological abnormality in systemic lupus erythematous. Anemia is found in approximately 50% of patients, with anemia of chronic disease being the most common form. Impaired response of the bone marrow to erythropoietin and sometimes presence of antibodies against erythropoietin may contribute to the pathogenesis of this type of anemia. Some Patients with systemic lupus erythematous may have autoimmune haemolytic anemia which usually belong to a distinct category, which is associated with anticardiolipin antibodies, antinuclear antibodies sometimes with anti Dsdna antibody. In patients with systemic lupus erythematous thrombosis, thrombocytopenia and renal involvement, often occur in the context of secondary antiphospholipid syndrome. Finally, as recently suggested, auto antibodies, T Lymphocytes and deregulation of the cytokines network can affect bone marrow erythopoiesis leading to anemia.

Case report:

A 35 years old female patient came to OPD with complaints of easy fatigability since 3 months which was gradual in onset and was progressive in nature. At onset she was having NYHA Grade 1 dyspnea which progressed over 3 months to grade 3 dyspnea at present. She had pallor on general examination and was also having yellowish tinge on the eyes. Rest of the general examination was normal. Cardiac and respiratory examination was not informative. On abdominal examination mild to moderate splenomegaly and mild hepatomegaly was found. No other positive clinical findings were present.

Patient was admitted to IPD for further evaluation. All routine investigation for anemia were send to pathology including complete blood count, peripheral smear examination, liver function test, ultrasonography etc.

After all routine reports came patient had Hb 6.4 gm% with normal total leukocyte and platelet count. On peripheral smear fragmented RBC's were noted that lead to suspicion of haemolytic anemia. Patient was further evaluated for anemia which showed highly elevated serum LDH and also positive direct coombs test that lead to conformation of haemolytic anemia.

To find out cause of the haemolytic anemia she was further evaluated for HCV and connective tissue disorder. Patient had negative HCV but she had positive antinuclear antibody and positive antiDsdna antibody. This lead to diagnosis of systemic lupus erythematous induced haemolytic anemia.

After the diagnosis patient was started with prednisolone 40 mg once a day and hydroxychloroquine 200 mg twice a day and was discharged home. After follow up after 15 days on complete blood count she had improved Hb 8.2gm%. After that she was kept on maintenance doses of prednisolone and hydroxychloroquine and was asked to follow up monthly in OPD.

Introduction

By incorporating haemocytopenias into the revised American College of Rheumatology criteria for systemic lupus erythematosus (SLE), the experts of the field have acknowledged that the "haematologic system" is frequently attacked in the setting of this disease. Although lymphopenia is the most frequent haematological disturbance in SLE, clinicians are often faced with the common problem of an anemic SLE patient (1-4).

Although it was initially suspected that anemia in SLE was a result of mainly antibody-induced damage of erythrocytes, evidence to date indicates that the causes of anemia in SLE vary and may be of immune or non-immune pathogenesis (1, 5-7)

(Table).

Table.Causes of anemia in patients with SLE

Anemia of chronic disease

Blood loss

Gastrointestinal loss, menorrhagias

Nutritional deficiencies

Iron,Folic acid, vitamin B12

Immune-mediated

Haemolysis, red cell aplasia, haemophagocytosis, aplastic anemia, pernicious anemia

Myelofibrosis

Uremia

Treatment induced

Microangiopathic haemolysis

Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, drugs

Hypersplenism

Infection

Myelodysplasia.

In this review, we focus on the nature, pathophysiologic mechanisms and causes of anemia, as well as the clinical approach and management of anemia in patients with SLE.

Autoimmune haemolytic anemia

Antibody-induced damage of blood cells by complement-dependent or independent mechanisms has long been considered a common pathogenetic mechanism for cytopenias in SLE. Evidence which restricts bona fide AHA in 5-10% of SLE patients with anemia, appears to contradict this hypothesis (1).

The pathogenesis of AHA should be reviewed within the fundamental immune disturbance of SLE. Interpreting how self-intracellular antigens become immunogens, so effective as to trigger and maintain a strong and prolonged autoantibody response, is both challenging and crucial. Genetic predispositions and defects in apoptosis, T cell function and complement or complement receptors are but a few of the numerous abnormalities which have been proposed to underlie lupus pathogenesis, predispose loss of self-tolerance and allow the production of pathogenic autoantibodies (8-11). In SLE the anti-erythrocyte antibody is mainly IgG of warm type and usually displays non-Rhesus specificity (1). Such antigens are expressed normally by human fetal erythrocytes, as early as 10 to12 weeks of life. It has been shown in NZB mice, an animal model for SLE, that autoreactive B cells can be sheltered from host erythrocytes entering the peritoneal cavity, an immune privileged compartment

that allows them to escape deletion and later produce anti-erythrocyte antibodies, with the appropriate T-cell assistance (12).

The precise specificity of the anti-erythrocyte antibodies for the majority of patients with SLE and AHA is undefined. The non-Rhesus specific IgG autoantibodies in patients with primary AHA have been found to react with either the band 3 anion transporter protein of membrane erythrocytes or with an epitope formed by band 3 protein and glycophorin A (13). NZB lupus prone mice produce antierythrocyte autoantibodies that exhibit anti-band 3 specificity (14). Interestingly, antiband 3 IgG antibodies are naturally formed in healthy individuals, possibly functioning as eliminators of senescent erythrocytes, which on aging express band 3 protein-derived neo-antigens (15). The relation between the naturally occurring and pathologic anti-band 3 autoantibodies remains an important, yet unanswered question.

One could hypothesize that such antigenic neo-epitopes, when exposed on senescent red cells, drive autoantibody responses, thereby triggering auto-hemolytic process.

This concept stems from considerable data suggesting that the generation and clearance of dead cells are important events that underlie the immunopathology of SLE in general (11).

Deficient clearance of dead cells is a critical pathogenetic feature of SLE. Macrophages from SLE patients were proven to be less phagocytic by prolonged clearance half time of Cr-labeled anti-IgG sensitized autologus erythrocytes (16). An interesting, yet unexplained, finding was that patients with SLE and AHA showed an acquired deficiency of either or both CD55 and CD59 erythrocytic expression, while SLE patients without AHA positively exhibited these molecules (17). Although the deficiency of these GPI-anchored proteins, whose role is to control complement activity, might contribute to hemolytic process by increasing the susceptibility to complement-mediated lysis, this defect seems to play an enhancing rather than a triggering role. Erythrocytes from patients with paroxysmal nocturnal hemoglobinuria are deficient in a membrane regulatory protein of complement, called decay accelerating factor. Moreover, a functional defect in a second membrane regulatory protein of complement, CR1 has also been hypothesized. In this context there are also some data about the loss of CR1 on erythocytes of SLE patients (18, 19). The loss of GPI-anchored structures might be responsible for some Coombs-negative haemolytic anemia cases in these patients.

In SLE patients, antibodies which react with negatively charged phospholipids such as cardiolipin and putative co-factors have been shown to correlate with venous and arterial thromboses, thrombocytopenia and recurrent fetal loss, a syndrome called secondary antiphospholipid syndrome (APS) (20). Among SLE patients, the prevalence of antiphospholipid antibodies is high, ranging from 12% to 30% for anticardiolipin (ACL), and 15% to 34% for lupus anticoagulant antibodies. Several studies of patients with SLE demonstrated a significant correlation between ACL or lupus anticoagulant and Coombs' positive hemolytic anemia (20-25). There is increasing evidence that ACL autoantibodies are not just a secondary phenomenon caused by haemolysis. They could also contribute to the pathogenesis of AHA by acting as anti-erythrocyte autoantibodies (26, 27).It is still unclear whether the presence of AHA worsens the outcome of SLE patients (3, 28). It has been suggested by one study group that lupus patients with AHA may have a more benign course, yet others found differences only in the prevalence of serositis (29, 30). Severe haemolytic anemia is rather rare and has been significantly associated with other organ involvement including the kidneys and central nervous system (31). In a retrospective case-control study of our department, when assessing the clinical picture, the immunological characteristics and the survival of 41 SLE patients with AHA, 2/3 of these patients were found to display autoimmune haemolysis at the onset of SLE (32). It was further revealed that patients with AHA secondary to SLE were more likely to have IgG ACL than controls. The frequency of IgG ACL in this SLE cohort with AHA was 74%, remarkably higher than that previously noted in unselected patients with SLE (33). In addition, many of these patients displayed renal involvement, thrombocytopenia and other manifestations of the APS. Thus, autoimmune haemolysis seems to be a marker for a subset of SLE patients with a higher prevalence of APS (34, 35).

Autoimmune hemolytic anemia in SLE Treatment: patients is seldom severe and rarely fatal as prednisolone is usually sufficient in controllling haemolysis. Should this treatment fail other forms of immunosuppression such as azathioprine and cyclophosphmide as well as danazole, intravenous immunoglobulin or anti-CD20 monoclonal antibody should be tried. Splenectomy should be considered only as a last resort given the poor response reported (36).

Pathophysiologic mechanisms underlying anemia of chronic disease in SLE

Patients suffering from chronic inflammatory disorders, commonly display ACD, a mild to moderate normocytic-hypochromic anemia the pathogenesis of which remains obscure (37). Insufficient supply of haemopoietic cells with EPO, along with their resistance to its proliferative action constitutes an important pathogenetic mechanism of ACD in several autoimmune diseases (38-40). The phenomenon can be attributed to the impaired EPO resulting from the inhibiting action of inflammatory cytokines such as IL-1, TNF-a, INF a, β and TGF-β (41). Experiments have shown that rat kidneys produce less EPO when exposed to IL-1 (42). In addition, over production of these cytokines has been associated with primary resistance of haemopoietic progenitors to the action of EPO (43-46).The presence of autoantibodies against EPO (anti-EPO) has been proposed as another possible cause of EPO deficiency . Although a correlation between anti- EPO antibodies and EPO levels was not detected in this study, underestimation of EPO measurement due to autoantibodies interference cannot be excluded in SLE patients, as proposed by Schett et al (47-49). The possible role of anti-EPO antibodies in the pathophysiology of ACD in SLE patients was studied by measuring the levels of EPO, as well as the presence of anti-EPO antibodies (45).This data suggested that patients with anti-EPO antibodies suffered from a more active disease, despite the fact that negative correlation between hemoglobin levels and presence of anti-EPO antibodies was not proven. However, the presence of anti-EPO antibodies was associated with active SLE and severe anemia in a previous study (50).

Clinical considerations. Conclusions.

Distinctly different therapeutic approaches are required for the multiple causes of anemia in patients with SLE. ACD is the most common form of anemia in these patients; AHA, IDA, drug-induced myelotoxicity, and anemia due to chronic renal failure are also often detected (1-3, 5,45). Aplastic anemia, PRCA, pernicious anemia, myelofibrosis, sideroblastic anemia, hemophagocytic syndrome, and thrombotic microangiopathy occur less frequently (51-56). Given the complexity of these patients' illnesses, a thorough history and physical examination is essential for placing the anemia in its proper context. In clinical practice, simple tests may help to diagnose the underlying cause of anemia in SLE patients. For example, if the reticulocyte count is raised, a hemolytic process or acute bleeding should be suspected. Diagnosis of warm-type hemolysis relies on the positive direct Coombs' test combined with reduction of haptoglobin. Increased serum creatinine and blood urea nitrogen levels would indicate poor renal function due to renal disease, which leads to poor secretion and lower serum levels of EPO. Frequently, however, the anemia in SLE patients is accompanied by a low reticulocyte count, reflecting a hypoproliferative state. An elevated MCV may be an indication of either vitamin B12, folate deficiency or the toxic effects of immunosuppressive agents. A low MCV typically indicates IDA or ACD. Patients with the ACD are characterized by reduced plasma iron and transferring concentrations, while iron stores, as reflected by plasma ferritin levels, are normal or even increased. The differential diagnosis between IDA and the ACD can

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now be readily made by measurement of the plasma transferrin receptor concentration and, ideally, determination of the plasma transferrin receptor-ferritin index. BM aspiration can be helpful in evaluating the hypoproliferative anemia, revealing deregulation of cellularity, absence of iron stores or megaloblastoid maturation, hemophagocytosis, PRCA, or sideroblastic anemia.

Based on published clinical trials, recombinant human erythropoietin (rHuEPO) therapy can be proved beneficial outside the settings of uremia. In every day practice, the use of rHuEPO should be limited to patients with symptomatic anemia and those who are transfusion-dependent or candidates for blood transfusion.However, few SLE patients have haemoglobin levels lower than 8 to 9 gr/dl and practically none of these patients is transfusion-dependent. Thus, although SLE patients with ACD may show excellent hematologic response to rHuEPO, there is little rationale for widespread treatment. Evidence has been provided that rHuEPO therapy is occasionally associated with anti-rHuEPO antibodies not only capable of inhibiting the exogenously administered rHuEPO but also of inhibiting endogenous EPO, causing PRCA (57).

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