Systemic Lupus Erythematosus with Autoimmune Hemolytic Anemia and Pure Red Cell Aplasia

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Abstract

Systemic lupus erythematosus (SLE)-associated autoimmune hemolytic anemia (AIHA) is common in clinical practice. However it is unusual when pure red cell aplasia (PRCA) is also presented in addition. Here we report such a case. A 31 year-old housewife has been pale for more than one year. Physically, she was pallor, with several small soft lymphnodes over both sides of neck, grade II/VI systolic murmur over apex, spleen just palpable, otherwise unremarkable including no evidence of joint lesion nor skin eruption. Hematologic and serologic studies disclosed evidence of AIHA, of which the underlying disease was suggestive to be SLE by the presence of AIHA and high titer of antinuclear antibody (ANA). Of particular interest was the occurrence of reticulocytopenia in the situation of hemolytic anemia. This was explained by the finding of depleted erythroid precursors in bone marrow which presented a picture of PRCA. The SLE-associated antibody may target the antigenic components which are shared by the red cells in peripheral blood and by the erythroid progenitors in bone marrow. In this way, the SLE patient may present with both AIHA and PRCA. (J Intern Med Taiwan 2004; 15: 134-138)

Key Words：Systemic lupus erythematosus (SLE), Autoimmune hemolytic anemia (AIHA), Pure red cell aplasia (PRCA), Antinuclear antibody (ANA)

Introduction

In ordinary circumstances, autoimmune hemolytic anemia (AIHA) is characterized by shortened red cell survival with compensated erythroid hyperplasia in marrow with ensuing reticulocytosis. But if it is complicated by bone marrow disease, decreased reticulocyte count will occur in disease of hemolytic anemia rather than reticulocytosis. Pure red cell aplasia (PRCA) is a disease recognized by severe normocytic, normochromic anemia associated with obviously depleted erythroid progenitors in otherwise normal marrow with resulting marked reticulocytopenia. Of which the causes are various, including congenital and acquired varieties. The

acquired form is frequently associated with parvovirus B19 infection, drug therapy, thymoma and other immunologic disorders etc. In systemic lupus erythematosus (SLE), the associated autoantibody may target the antigenic components which are shared by the red cells in peripheral blood and by the erythroid progenitors in marrow. In this situation, coexistence of both AIHA and PRCA may occur in SLE patient. Since simultaneous occurrence of both AIHA and PRCA is uncommon in clinical practice, herein we report a case as such in SLE patient.

Case Report

A 31 year-old house wife was admitted because of pale for more than one year. She had been well until one year ago when she gradually became pale, weakness and frequently getting dyspnea. She was told to be anemic but the effect of treatment was in vain. There was no fever or taking any drug prior to the onset of her illness. Past history was unremarkable.

Physically, she looked pale, several soft movable non-tender peanut-sized lymphnodes were noted in both sides of neck, there was grade II/VI systolic murmur over apex, spleen was just palpable. Otherwise, there was negative finding including no jaundice, no friction rub of chest, no sign of congestive heart failure, no neurologic condition, nor signs of skin eruption, arthritis or gangrene of finger tips.

Laboratory examination showed: WBC 6000/cumm, with normal differential count; Hb 4.7 g/dl, MCV 90 fl, reticulocyte count 0.2%; platelet 275,000/cumm ; RBC morphology in blood smear: normocytic, normochromic, no aniso-poikilocytosis, no RBC fragments, no polychromatophilia, no normoblast; urine routine: albumin trace, OB (++), urine sediment normal including RBC：0~1/ HPF; stool routine negative; serum albumin 4.2 g/dl, globulin 5.6 g/dl, GOT 59 U, GPT 19 U, LDH 2582 W.U. (normal range 210~450 W.U.), ALP 37 IU/L (normal range 20~78 IU/L), total bilirubin 1.9 mg/dl, direct bilirubin 0.66 mg/dl, creatinine and electrolyte within normal limits; serum protein electrophoresis：polyclonal gammopathy.

Chest X-ray：negative finding including no mediastinal enlargement.

Abdominal echo disclosed mild splenomegaly, otherwise negative finding.

Bone marrow study showed normal cellularity, normoblast severely depleted (3%), compatible with pure red cell aplasia, otherwise unremarkable (Fig. 1).

From these initial informations listed above, she was presumptively considered as a case of hemolytic anemia. Further data revealed: heptoglobin < 20 mg/dl (normal range 175.7 +/- 63.8 mg/dl), G6PD 20’ (normal <60’) , hemoglobin electrophoresis within normal limits, sugar water test negative, cold agglutinin: 1: 40, direct Coombs'test: (+), anti-IgG (+), anti-C3d (+); ANA 1: 2560 (+), coarse speckle type, anti-ds-DNA negative, LE cell not found, C3 58 mg/dl, C4 15.2 mg/dl,

Donath-Landsteiner antibody negative.
The diagnosis was SLE presenting with both AIHA and PRCA.
Prednisolone 60 mg daily was given with excellent effect. The bone marrow aspiration was followed one month later. Normoblast got increased from 3% to 28% with reticulocyte count from 0.2 % to 4.8% (Fig. 2). Other follow-up items included: Hb 12.0 g/dl, ESR 22 mm/1h, C3 80 mg/dl and C4 17.1 mg/dl. Additional serologic studies were performed at this time with the results of anti-ENA (+), anti-RNP < 1:8(+) and anti-Sm (-). The patient was symptom-free. The steroid began to be tapered one month after treatment and kept low dose maintenance subsequently.

Discussion

From the initial laboratory data, the patient had hemoglobinuria, increased indirect bilirubin and LDH. Hemolytic anemia was highly suspected which was further supported by the finding of markedly decreased heptoglobin examined later. In the setting of hemolytic anemia, there are several points remained to be discussed. The questions would be: (1) why did it present with reticulocytopenia in the situation of hemolytic anemia? (2) was the hemolysis caused by intracorpuscular or extracorpuscular mechanisms? and finally (3) what was the underlying disease responsible for this events? The first question could be clearly settled by the finding of pure red cell aplasia shown in bone marrow study 1. Further exploration of the hemolytic anemia revealed the occurrence of extracorpuscular disease evidenced by the finding of positive DAT (direct antiglobulin test) with both warm and cold autoantibodies which made the diagnosis of AIHA.
The diagnostic criteria of SLE revised in 1982 by ARA consisted of 11 items 2. A patient can be definitely diagnosed as SLE if any four or more of the 11 criteriae are met. Our patient had only two of it ---- AIHA and high titer of ANA . Positive ANA is not specific for SLE but has only a predictive value of 57% for lupus 3. The presence of anti-ds-DNA and/ or anti-Sm antibody are more specific for SLE 4. As to the titer of ANA, if ANA titer is greater than 1:80, it has a positive predictive value of 72% for SLE, and if greater than 1: 320, it is of 80% 3. If ANA titer is greater than 1: 2560, as our case had been, three possibilities will be considered---- these are SLE, progressive systemic sclerosis (PSS) and mixed connective disease (MCTD). There was neither skin thickening proximal to the wrist nor evidence of Raynaud's phenomena during the course of disease in our case that made PSS unlikely 5. Low titer of anti-RNP is not like MCTD 4, but it was difficult to interpret in our patient because the antibody to RNP was studied after steroid treatment. According to the statements that AIHA is very unusual in PSS, RA, polymyositis and dermatomyositis and is rarely seen in other connective tissue diseases except SLE 5, lupus is the most likely diagnosis.
It is interest to show reticulocytopenia and depleted normoblast in marrow in cases of

AIHA, but it may occur in some way: red cells in peripheral blood and erythroid progenitors in marrow may share the same antigenic components which act as targets of the antibodies 6. How does it assess the antibody inhibiting the proliferation and differentiation of erythroid precursor cells in marrow? The following principle can help resolve the problem: buffy coat cells from normal marrow aspirates are cultured in plasma clots in the presence of erythropoietin and other tissue culture medium 7. By adding patient's serum or eluates of patient's red cells, the number of erythroid colonies will be depressed as compared with that of the control 6. Thus, it proves the auto-antibody of the patient acting on normoblast in marrow, leading to PRCA.

The pathophysiology of PRCA is heterogeneous. There are congenital and acquired forms. Acquired PRCA may be caused by parvovirus B19 infection which runs a self-limited course in a majority of patients. Most cases of PRCA can be attributed to immunologic interactions. The immune-associated PRCA may be either antibody-mediated or T cell/ NK cell-mediated disorders. The former consists of thymoma 8, SLE 9, RA 10 and lymphoma with various mechanisms, such as complement-mediated lysis of red cell progenitors, formation of antibody-EPO immune complex, blocking EPO receptors, T cell dysfunction with ensuing increased Th2 subset resulting in increased production of autoantibody 11, inhibiting hemoglobin synthesis or blocking differentiation of BFU-E in vitro 9,12. Whereas the T cell/ NK cell-mediated variety presents with status of large granular lymphocyte (LGL) expansion in disease of CLL, LGL leukemia and lymphoma. Of which the pathogenesis is triggering cytolysis against normoblast either via TCR recognizing the ligands expressed by the normoblast or via antibody against red cell progenitors with the antibody binding to Fc receptor on the LGLs 12. The strategy of treatment is management of the underlying disease and uses steroid as initial immunosuppressive agent. If it is not effective, the other options of choice will be endoxan, MTX, cyclosporine, antithymocyte globulin or plasmapheresis according to the clinical situations 9,13-14.

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Fig.1. Bone marrow picture before treatment ---- predominantly of myeloid cells with almost depleted erythroid progenitors.

Fig.2. Clinical course of the patient with initial hemoglobin level and reticulocyte count in admission which got greatly improved after the institution of pred (prednisolone)60 mg daily. The B. T. (PRBC transfusion) favored the patient little. Hb: hemoglobin, Hp: heptoglobin, Ret: reticulocyte count (%)

系統性紅斑性狼瘡合併自體免疫溶血性貧血及紅血球再生不良症

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摘　　要

系統性紅斑性狼瘡合併自體免疫溶血性貧血，在臨床上並不少見，但是如果另外又伴有純紅血球再生不良症時，則不多見；在此我們就報告這麼一個病例。一位卅一歲的家庭主婦，面色蒼白已經一年，既往歷沒什麼特別之處。她看來臉色蒼白，兩側頸部有多個小而軟的淋巴結，心尖處有第二級收縮期雜音，脾尖可觸診到；其他則無異狀，例如無關節病變，亦無皮疹。血液及血清學檢查顯示有自體免疫性溶血性貧血，而其基本的病因乃是系統性紅斑性狼瘡，後者的診斷，是依據病患表現的自體免疫性溶血性貧血及高效價的抗核抗體來推論的。有一點比較特別的是：在溶血性貧血的病況下，居然出現網狀紅血球缺乏的徵相；這個怪異的表現，乃肇因於骨髓中紅血球母細胞罄盡，也就是所謂的純紅血球再生不良症所致。周邊血的紅血球和骨髓內的紅血球母細胞，可擁有某種相同的抗原，它是系統性紅斑性狼瘡相關抗體的標的物，因之，引起紅血球及其母細胞的破壞。以此之故，系統性紅斑性狼瘡的病人，可以同時表現自體免疫性溶血性貧血及純紅血球再生不良症的徵候。