Case report

A Case Report Of Megaloblastic Anemia Associated With Immuno – Hemolytic Anemia In an Old Lady

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Abstract Although, megaloblastic anemia is a common entity, association of pernicious anemia and autoimmune hemolytic anemia with two different mechanisms of hemolysis (ineffective erythropoesis and immune mechanism) is a very rare condition with no case reported in the geriatric population. We, here present a case of an 80-year-old female who was admitted to the hospital with generalized weakness. At admission, patient was found to have macrocytic anemia, with a high serum LDH. Also, patient had positive antibodies to intrinsic factor and parietal cells, with a decreased level of vitamin B12 and peripheral smear compatible for pernicious anemia. Treatment with vitamin B12 and folic acid was initiated which turned out to be ineffective. At this time cold agglutinins were found to be positive. We proposed a possibility of pernicious anemia in association with autoimmune hemolytic anemia. So the patient was started on methylprednisone in addition to vitamin B12 therapy. This combination was successful in improving her hemoglobin.

Introduction

Only several cases of synchronous presentation of pernicious anemia and autoimmune hemolytic anemia (AIHA) have been described [1-5]. There are also rare descriptions of coexistence of pernicious anemia and another autoimmune disease, e.g., autoimmune disease of thyroid or that of connective tissues [6, 7]. The annual incidence of AIHA is 1/80,000 to 2.6/100,000 in general population. Approximately 18% of AIHA may be caused by medications, 75% of patients with AIHA have secondary AIHA combined with another disease, and 25% have primary AIHA. According to thermal characteristics of autoantibodies, AIHA is classified as "warm", usually of IgG class, and as "cold" when the highest reactivity of autoantibodies, usually of IgM class, is recorded at 32℃ [8]. The mechanism leading to immune hemolysis depends on the concentration and biological characteristics of antibodies, i. e. class, subclass and complement activation. A basic test for AIHA is direct antiglobulin test (DAT, Coombs test), which shows the presence of antibodies on erythrocyte membrane. Although never an obligatory part of pre-transfusion testing, DAT enables early detection of immune response to a recent transfusion, diagnosis of hemolytic disease in a newborn, and suspected autoimmune or drug induced hemolysis. Positive DAT should never be identified with the diagnosis of AIHA. In the same way, negative DAT does not necessarily exclude immunologically induced hemolysis. The diagnosis of AIHA with negative DAT may be established when the patient has laboratory and clinical signs of hemolysis, and non-immune causes have been excluded. Approximately 60% of patients with warm AIHA also have circulating autoantibodies in serum, i.e. positive indirect antiglobulin test (IAT). Many patients have only autoantibodies in serum, but some (30%) also have alloantibodies. In most cases with cold AIHA (which accounts for 10%-15% of all AIHA), only the complement is present on erythrocytes. In warm AIHA, the proportion of IgG is 30%-40%, in combination with C3 40%-50%, and of the complement alone 10%-20%. The proportion of DAT-negative AIHA is 2%-4% [9]. Megaloblastic anemia (including a subclass of autoimmune pernicious anemia) is disorders of DNA synthesis, for which vitamin B12 and folic acid are essential as coenzymes. RNA synthesis is continued and faster maturation of the cytoplasm occurs, while the nucleus is relatively immature (a synchronism in maturation of the nucleus and cytoplasm). The first sign of Megaloblastic anemia is an increase in the erythrocyte mean corpuscular volume (MCV >100 fL) with appearance of macrocytes in peripheral blood smear and hemolysis in the bone marrow compartment due to ineffective erythropoiesis. In advanced megaloblastic anemia, pancytopenia may occur. Except for MCV, high red blood cell distribution width (RDW) showing the presence of anisocytosis is also very important. At the same time, the erythrocyte histogram analysis enables recognition of unimodal and bimodal curves showing changes in cellular population[10]. Apart from these parameters, an urgent microscopic check-up of erythrocyte morphology (exclusion of schistocytes, target cells, etc.) is needed for differentiation from other

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hemolytic anemias.

Case Report

A female patient aged 80 years was admitted to the hospital for generalized weakness and exhaustion. She had history of anemia with multiple blood transfusions and dementia. At admission, the patient was communicative, pale, adynmic and eupneic (14 respiration/min). Her blood pressure was 140/88 mm Hg, pulse 72/min. On palpation, there was no thyroid gland enlargement, peripheral lymph node or hepato-spleenomegaly. On auscultation, there were normal respiratory sounds and 2/6 systolic murmur, which could be heard all over the precordium. Laboratory tests on admission were as follows: Hb 3.2 g/L, Hct 7.7, WBC 4.8 and platelet 82. Renal function tests were in normal limits and liver function revealed normal values except an increased indirect bilirubin. Electrolytes, coagulation profile, ammonia levels and troponins also came out to be normal. Macroovalocytosis, anisocytosis, poikilocytosis, hyperchromatism and neutrophils with hyper-segmented nuclei were found in peripheral blood smear (Fig 1). Serum LDH concentration was high with low serum concentration of vitamin B12 and normal serum concentration folic acid levels. Reticulocyte count was found to be 24.9.

PRBC transfusion was ordered for the severe anemia, but patient could not receive it due to unavailability of compatible blood. Patient had multiple antibodies possibly secondary to multiple transfusions in past. The Hb dropped the next day to 2.3. On second day, patient received 4 units of PRBC and her Hb trended up to 8.5. The work up for anemia revealed normal iron, decreased iron binding capacity and transferrin and an increased iron saturation. Other labs ordered showed increased levels of anti-parietal antibodies and positive antibodies against Intrinsic factor. The clinical and pathological picture was suggestive of megaloblastic anemia secondary to vitamin B12 deficiency so the patient was started on vitamin B12 therapy with folic acid.

After 8 days of vitamin B12 therapy, hemoglobin concentration and erythrocyte count deteriorated, as follows: Hb 5.4 g/L, MCV 123.4 fL, MCH 42.1 pg, MCHC 341 g/L, RDW 30.3, Rtc 26%, PLT 76, and WBC 6.6. The patient's clinical status was unchanged. Further, work up revealed positive cold agglutinin. Therapeutic strategy was changed because the finding of immune hemolysis due to AIHA was obviously coexisting synchronously with megaloblastic anemia. Methylprednisolone 120 mg per day intravenously (i.v.) was administered and after 48 hours the clinical status improved: Hb 8.0 g/L, MCV 101.0 fL, MCHC 331 g/L, RDW 22.3%, Rtc 12, PLT 441, and WBC 6.7. Therapy with daily methylprednisolone and vitamin B12, added with folic acid supplementation was continued and it was followed by continuous rise in hemoglobin level.

Patient's one marrow Biopsy revealed mild megakaryotic hyperplasia and no acute leukemia, myelodysplasia, lymphoma or myeloma and storage iron was present (Fig 2). Flow cytommetry

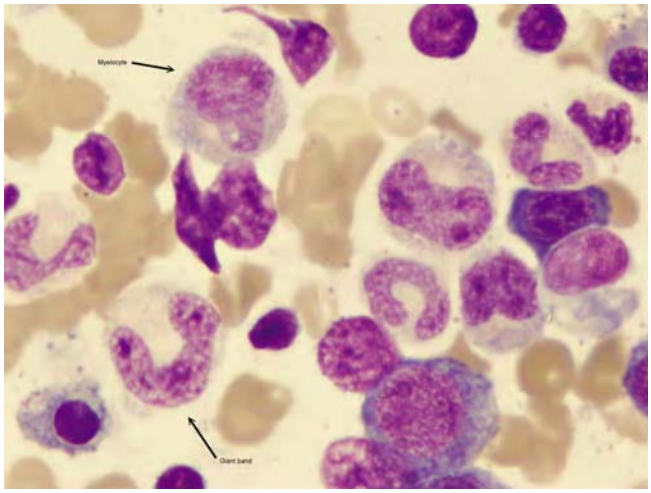

Fig.1 Peripheral Smear

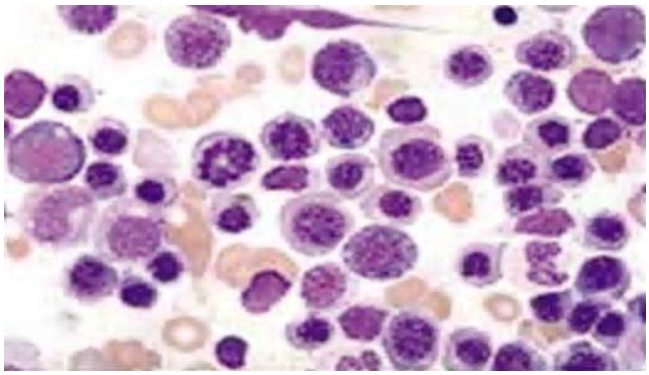

Fig.2 Bone Marrow

was also ordered, which was negative for any malignancy.

At discharge, cold agglutinin was still positive; MCV was 98 fL, Hb 9.1 g/L, while LDH and reticulocytes were slightly elevated. And patient Hemoglobin remained stable over steroid therapy.

Discussion

On admission, the clinical picture, macrocytic anemia, high values of LDH and low serum concentration of vitamin B12, with positive antibodies to intrinsic factor and parietal cells were highly suggestive of pernicious anemia. The administration of vitamin B12 and folic acid was justified. Four additional points support the thesis of pernicious megaloblastic anemia: (1) decrease in serum LDH concentration after 36 h of vitamin B12 administration, probably due to reduced early hemolysis in the bone marrow compartment. High concentration of LDH is due to inefficient erythropoiesis, a large number of megaloblasts in the bone marrow deteriorate, while megalocytes of poor quality and other abnormal erythrocytes are hemolyzed in peripheral blood vessels, producing a

high concentration of LDH and indirect bilirubin. Such characteristically high LDH values were also found in our patient; (2) pathognomonic reticulocyte count of 24.9 after 8 days of vitamin B12 therapy; (3) continuous reduction and eventually normalization of erythrocyte MCV on vitamin B12 therapy; and (4) high RDW value, characteristic of macrocytic anemia is primarily associated with three conditions: ① vitamin B12 deficiency, pernicious anemia and post-gastrectomy intestinal disorders; ② folate deficiency: dietary deficiency, possible in vegetarians, folate destroyed by prolonged cooking, impaired absorption: sprue, increased folate requirements in pregnancy, infancy, hemolytic anemia, and malignancy; and ③ hemolytic anemia that was also diagnosed but simultaneously presented in combination with vitamin B12 deficiency.

Schilling test, serum homocysteine and methylmalonic acid were not done due to technical reasons, but were not crucial in the diagnostic procedure. Bone marrow aspiration was performed during the of hospital stay, after obtaining the patient's consent. In the mean time, hematopoiesis normalized with vitamin B12 treatment and pathognomonic cytomorphological signs of megaloblastic hematopoiesis disappeared.

We proposed that the patient suffered from a combination of two autoimmune diseases, pernicious anemia and secondary autoimmune hemolytic anemia, which, in our opinion, occurred in the context of attenuation of immune surveillance. Regarding cold agglutinin induced hemolytic anemia many patients do not need transfusion therapy. Of course, in case of severe and life-threatening anemia, transfusion therapy is necessary like in our patient. Our patient did not receive transfusion after the initial stabilization because of excellent response to corticosteroids and stable cardiopulmonary status. The underlying disease, if present, should be primarily treated. Before transfusion, corticosteroid therapy should be initiated (for example, prednisolone 1.5-2.0 g/kg). Approximately 80% of patients respond well to therapy and complete remission of the disease occurs in 20% of patients. The same outcome of corticosteroid therapy was observed in our patient.

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