

A Case of *Plasmodium vivax* Malaria Associated with Autoimmune Hemolytic Anemia

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삼일열 말라리아와 연관된 자가 면역 용혈성 빈혈 1예

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Anemia associated with *Plasmodium vivax* (*P. vivax*) malaria occurs as a result of the lysis of red cells by schizonts, bone marrow suppression, and splenic sequestration. A 20-year-old man presented with fever and anemia. He was diagnosed with *P. vivax* malaria with a positive direct antiglobulin test and treated with antimalarial medication for 2 weeks. He recovered without sequelae. we suggest that autoimmune hemolytic anemia should be considered as one of cause of anemia in *P. vivax* malaria.

Key Words : *Plasmodium vivax* malaria, Autoimmune hemolytic anemia, Direct antiglobulin test

autoimmune hemolytic anemia.

INTRODUCTION

Anemia associated with *P. vivax* malaria occurs as a result of the lysis of red cells by schizonts, bone marrow suppression, and splenic sequestration(1). In *Plasmodium falciparum* (*P. falciparum*) malaria, the extent of hemolysis is much greater than what we experience in other parasite induced hemolysis and combined mechanism with immune mediated hemolysis has been suggested(3). Positive results in DAGT were been found only in a minority of patients and it was suggested that complement or immunoglobulin-mediated immune complex formation contribute to hemolysis in *P. falciparum* malaria infection(4). But *P. vivax* malaria with direct antiglobulin reaction has not been reported. We encountered a patient with *P. vivax* malaria associated with

CASE REPORT

A 20-year-old man was admitted to the hospital with fever for several days. He was previously healthy and had no specific medical history. Upon admission his blood pressure was 110/80 mmHg, pulse rate was 84/min, respiration rate was 15/min, and body temperature was 38 °C. He appeared mildly pale but was not icteric. His spleen was palpable 5 cm below the left costal margin and was moderately firm and nontender. No hepatic enlargement or lymphadenopathy were noted.

Laboratory findings included the following: hemoglobin level, 9.6 g/dL, with normocytic normochromic indices; leukocyte count, 3,600/ μ L, with 33% neutrophil (segmented form plus band form), 57.2% lymphocytes and 9.8% monocytes; platelet count 69,000/ μ L; erythrocyte sedimentation rate, 35 mm/h; haptoglobin 8 mg/dL; and total serum bilirubin 2.2 mg/dL. The VDRL test gave a negative result. The peripheral blood smear showed a few spherocytes and occasional malaria parasites. The

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Bioline P.f/P.v[®] (SD Inc, Yongin, Korea) test (a dipstick bearing monoclonal antibodies against the intracellular metabolic enzyme, parasite lactate dehydrogenase) gave a positive result. Antinuclear antibodies of speckled type were detected. Rheumatoid factor was not detected, and the C3 level was within normal limits, at 72 mg/dL. The direct/indirect antiglobulin tests (DAGT/IAGT) were performed with a broad-spectrum Coombs' reagent and gave all positive results. Unfortunately, but subclass test associated with DAGT was not performed.

He was diagnosed with *P. vivax* malaria associated with autoimmune hemolytic anemia and was treated with antimalarial medication for 2 weeks. The use of primaquine (a dose of 0.25 mg of the base/kg body weight per os) for fourteen days to overlap with chloroquine (initially in a dose of 10 mg of the base/kg body weight per os. This was followed by additional doses of 5 mg/kg after 6–8 h, and on the following days 2 and 3). Laboratory findings on 8th admission day included the following: hemoglobin level, 11.0 g/dL; leukocyte count, 7,700/ μ L, with 45.8% neutrophil (segmented form plus bands form), 49.5% lymphocytes and 4.7% monocytes; platelet count 318,000/ μ L; and total serum bilirubin 0.5 mg/dL. He fully recovered without sequelae.

DISCUSSION

P. vivax, the causative agent of vivax malaria, is the second most common species of malaria with a yearly estimate of 35 million cases worldwide(5). Anemia has frequently been associated with malaria, and its rate of occurrence depends on the age group and endemic region of malaria transmission. Traditionally, *P. falciparum* infection has been considered to produce anemia more frequently and with more severe degree than infections caused by *P. vivax*(6). However, recent reports have shown contrasting evidence demonstrating that *P. vivax* malaria may be associated with higher frequency and more severe degree of anemia(7–9).

The anemia in *P. vivax* malaria is caused by hemolysis, reduced cell deformity of parasitized and non-parasitized erythrocytes, increased splenic clearance, and a variable degree of bone marrow dyserythropoiesis(1).

In *P. falciparum* malaria, the extent of hemolysis is much greater than what we experience in other parasite induced hemolysis and combined mechanism with immune mediated hemolysis has been suggested(2). Immune hemolytic anemia is mediated by antibodies directed against antigens on the red blood cell surface. Microspherocytes on peripheral blood on a peripheral smear and a positive direct antiglobulin test (DAGT) are the characteristic findings(3).

Along with anemia, a characteristic laboratory feature of hemolysis is reticulocytosis, a normal response of the bone marrow to the peripheral loss of red blood cells. In the absence of concomitant bone marrow disease, a brisk reticulocytosis should be observed within three to five days after a decline in hemoglobin(3). In our case, because of technical error, reticulocyte count was not ascertained.

Review of the peripheral blood smear is a critical step in the evaluation of any anemia(3). If spherocytes are observed, immune hemolysis or hereditary spherocytosis should be contemplated. In this case, the peripheral blood film showed a few spherocytes and occasional malaria parasites. Spherocytes, characterized by absence of central pallor, are found in both autoimmune hemolytic anemia and hereditary spherocytosis. These cells, which have decreased deformability compared with normal red blood cells, are trapped in the splenic sinusoids and removed from circulation(10).

The destruction of red blood cells is characterized by increased unconjugated bilirubin, increased lactate dehydrogenase, and decreased haptoglobin levels. hemoglobin is converted into unconjugated bilirubin in the spleen or may be bound in the plasma by haptoglobin. The hemoglobin-haptoglobin complex is cleared quickly by the liver, leading to low or undetectable haptoglobin levels(11). In this case, low haptoglobin level was detected.

Once the diagnosis of hemolysis is made on the basis of laboratory and peripheral smear findings, it is necessary to determine the etiology. In this case, spherocytes on peripheral blood smear and positive DAGT suggested immune hemolytic anemia. Immune hemolytic anemia is classified as autoimmune, alloimmune, or

drug-induced, based on the antigen that stimulates antibody- or complement-mediated destruction of red blood cells(3). The direct antiglobulin test (DAGT), also known as the direct Coombs' test, demonstrates the presence of antibodies or complement on the surface of red blood cells and is the hallmark of autoimmune hemolysis. The patient's red blood cells are mixed with rabbit or mouse antibodies against human IgG or C3. Agglutination of the patient's antibody- or complement-coated red blood cells by anti-IgG or anti-C3 serum constitutes a positive test. Red blood cell agglutination with anti-IgG serum reflects warm autoimmune hemolytic anemia (AIHA), while a positive anti-C3 DAGT occurs in cold AIHA(12). In this case, direct/indirect antiglobulin tests (DAGT/IAGT) were performed with a broad-spectrum Coombs reagent and gave all positive results. But subclass test associated with DAGT was not performed.

Although most cases of autoimmune hemolysis are idiopathic, potential causes should always be sought. Warm AIHA also is associated with autoimmune diseases (e.g., systemic lupus erythematosus), while cold AIHA may occur following infections, particularly infectious mononucleosis and *Mycoplasma pneumoniae* infection(3). Malaria is the classic example of direct red blood cell parasitization. Plasmodium species, introduced by the Anopheles mosquito, invade red blood cells and initiate a cycle of cell lysis and further parasitization. Both the cellular invasion and the metabolic activity of the parasite alter the cell membrane, leading to splenic sequestration(13).

Positive results in DAGT were been found only in a minority of patients and it was suggested that complement or immunoglobulin-mediated immune complex formation contribute to hemolysis in *P. falciparum* malaria patients and suggested that complement or immunoglobulin-mediated immune complex formation contributes to the hemolysis of *P. falciparum* malaria infection(4). But *P. vivax* malaria with direct antiglobulin reactions has not been reported. So we suggest that autoimmune hemolytic anemia should be considered as one of cause of anemia in *P. vivax* malaria.

요 약

삼일열 말라리아에서 발생하는 빈혈은 말라리아 본열에 의한 적혈구 용혈, 골수억제 그리고 적혈구의 비장에서의 격리에 의해 발생한다. 20세 남자 환자가 그 열과 빈혈을 주소로 내원하였다. 직접 항글로불린 검사에 양성 소견을 동반한 삼일열 말라리아 환자였고 2주 일간의 항말라리아 약제를 복용한 후에 호응 없이 회복되었다. 상기 증례를 살펴보면 삼일열 말라리아에서 발생하는 빈혈의 원인으로 자각면역 용혈성 빈혈이 반드시 고려되어야 할 것으로 생각된다.

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