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Case Report

Internal Medicine Section

Paroxysmal Nocturnal Haemoglobinuria Masquerading as Malaria: A Case Report

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ABSTRACT

Paroxysmal Nocturnal Haemoglobinuria (PNH) is a rare type of acquired Haemolytic anaemia that is described as a triad of acquired intravascular Haemolysis, venous thrombosis and anaemia with pancytopenia sometimes due to bone marrow failure. However the classical triad may not be observed at once and fever due to leucocytopenia may confuse the clinical picture. Since this is a rare disease, other epidemiologically common causes may be attributed to the illness. We report a case of PNH with a rare association of malaria due to Falciparum and Vivax species which was undiagnosed for 6 years in a young man.

Keywords: Anaemia, CD55, CD59

CASE REPORT

An 18-year-old male student from Belagavi district of Karnataka state came to our medical college hospital with a history of recurrent episodes of intermittent fever with chills, rigors, sweating, anorexia and easy fatigability for eight days. Past history revealed that, six years ago he had experienced similar symptoms during which he was diagnosed as having malaria by card test in a private hospital followed by confirmation of *Plasmodium vivax* and *Plasmodium falciparum* infection by thick and thin smears. Quantitative Buffy coat in a government taluka hospital had also confirmed malaria. During his out-patient visit 8 months prior to the present admission, he was diagnosed as having *Plasmodium vivax* on his peripheral smear. There were no similar complaints among his family members. He has one sibling who is healthy. His mother is on treatment for hypothyroidism.

On clinical examination, he was severely anaemic and had mild jaundice. There was no hepato-splenomegaly, lymphadenopathy or bleeding tendency. His haemoglobin was 5.1g%, total white blood cell count 2900 cells/cubic mm, differential count predominantly lymphocytic (50%), reticulocyte count 4%, mean cell volume 80.3%, mean cellular haemoglobin 21.8 picograms and erythrocyte sedimentation rate 90 at one hour. Peripheral smear revealed severe anisopoikilocytosis, both macrocytes and microcytes with tear drop cells, pencil shaped cells, relative lymphocytosis and adequate platelets. Urine and stool examination was normal and there were no abnormal components. Bilirubin and serum lactic dehydrogenase levels were suggestive of Haemolysis. Ultrasound examination of abdomen was normal and there were no gall stones.

Keeping in mind his past laboratory findings and correlating them with his clinical features, he was diagnosed as a case of malaria with severe anaemia and treated with chloroquin, primaquin, parenteral iron sucrose, folic acid & methylcobalamine. His haemoglobin increased to 8g % in 6 weeks with regular haematinics.

On follow up, patient had recurrence of similar symptoms and when subjected for urine routine examination was found to have RBCs. He developed pancytopenia. His peripheral smears were negative for malaria. He had evidence of Haemolysis. Bone marrow was hypercellular with megaloblastic changes. Haemoglobin electrophoresis was normal. Serum Vitamin B12 was normal but red cell folate was decreased. Coomb's test was normal. He complained of passing cola coloured urine. As the Haemolytic picture could not be explained this time, he was referred to a haematologist.

The following results were obtained

Urine Haemosiderin was positive.

Bone-marrow had hypercellularity with megaloblastic erythropoiesis.

There was no increase in CD-34 and c-kit expressing precursors.

Bone –marrow iron staining revealed deficiency of stores.

Acid HAM test was positive (+++),

Sucrose Lysis test was positive (42%),

Anti MIRL (Membrane Inhibitor of Reactive Lysis) was positive (++) and anti DAF (Decay Accelerating Factor) was positive (++),

Flow-cytometry for PNH

65.8% of neutrophils & 73.3% of RBCs were negative for CD 55

81.9% of neutrophils & 82.9% of RBCs were negative for CD 59.

{For diagnosis of PNH, over 3% of RBCs and neutrophils should be negative for CD 55 & CD 59}[1]

Patient was finally diagnosed to be having paroxysmal nocturnal Haemoglobinuria (PNH) with iron deficiency. He was prescribed iron supplements and prednisolone. He could not afford eculizumab or bone marrow transplantation.

After starting this treatment he developed severe abdominal pain and Haemoglobinuria. Ultrasound examination of abdomen revealed no evidence of venous thrombosis. Prednisolone was stopped and blood transfusions were given.

DISCUSSION

PNH is an acquired chronic Haemolytic anaemia characterized by intravascular Haemolysis, pancytopenia and venous thrombosis. CD55 and CD59 on the surface of red blood cells (RBC) protect them from the membrane attack complex generated by complement activation. Somatic mutation in *PIG-A gene* causes a deficiency of glycosylphosphatidylinositol (GPI), a glycolipid that anchors these proteins on to the cell membrane. Lack of GPI causes loss of CD55 and CD59 from the cell surface making them prone for Haemolysis usually by the cascade of complement activation by alternate pathway. Sometimes, activation of the classical pathway by infection induced antigen-antibody complexes precipitates or worsens haemolysis [1].

The classical presentation of nocturnal episodic haemolysis that alarms the patient on the subsequent morning is seen in only 25% of patients, the commoner presentation being chronic anaemia and listlessness. The disease is rare with a prevalence of 1to 5 per

million people. It occurs in all age groups though more often seen in the middle age [1].

Our patient was a young boy who was treated for chronic anaemia for 6 years which was attributed to malaria. He was only 12-year-old when his anaemia was noticed. An erroneous diagnosis is apparently unlikely because the diagnosis was confirmed in at least three hospitals by different methods.

Malaria is known to affect haemopoietic cells by direct inhibition of multiplication of precursors and their differentiation. It has been demonstrated in-vitro on cord-blood-derived CD34+ cells that Vivax inhibits erythropoiesis. Haemozoin derived from Falciparum also induces anaemia by interfering with erythropoiesis. Chemokines induced by malaria can cause dyserythropoiesis. Bone marrow examination in malaria has demonstrated abnormal appearance of precursors including nuclear abnormalities [2], however there is no proof regarding the induction of mutations causing PNH by malaria parasite.

The malarial parasite on its entry into the red cell ensheaths itself in a semipermeable membrane called the parasitophorous vacuolar membrane. It then forms a network of tubules connecting this vacuole to the sub membrane structures called Maurer's clefts for transport of its proteins to the surface. These proteins induce an immune response causing the destruction of the red cell and release of merozoites to repeat the cycle again. Some of these proteins cause immune-destruction of uninfected red cells also and induce cell surface changes that attract complement mediated lysis [3]. An acquired deficiency of CD55 and CD59 is known to occur in malaria. These red cell surface changes referred to as "The battle scars" by Waitumbi J et al., predispose red blood cells (both infected and uninfected) to early phagocytosis and /or complement mediated lysis. However, the amount of reduction required for diagnosing PNH is more [3-5].

Age related changes are known to occur in the CD55 and CD59 in children who reside in malaria endemic areas. These reductions in the markers reach at 1 to 2 years of age. Reduction of these markers at this age predisposes them to severe malaria- related-anaemia in holoendemic areas by immunological mechanisms and complement mediated lysis of infected and uninfected cells alike [6]. We cannot presume the age at which our patient developed PNH that predisposed him to develop malaria infection.

Though it is known that CD55 and CD59 are un-necessary for the entry of plasmodium into the red cells, the infectivity of *Plasmodium Falciparum* into PNH RBCs is slightly more than in normal RBCs contrary to the assumption that Haemolytic anaemia confers a survival benefit against malaria. This has been demonstrated in a study that was conducted by infecting in-vitro, the red cells derived from a PNH patient and comparing it with normal red cells [7].

There is a case report mentioning the association of PNH and malaria in 1951 [8], but an abstract is not available of the same. There is also a report of two other similar cases in 1945 in which the author mentions two cases of PNH with malaria, one of which presented with black-water fever [9]. The cases discussed by that author had episodic Haemolysis, anaemia and early morning wine red urine. After 1951, an association of malaria with paroxysmal nocturnal Haemoglobinuria has not been reported. To the best of our knowledge, this is the only recent case-report of the occurrence of PNH in a patient who had malaria after the reports in 1945 and 1951.

CONCLUSION

The rarity of reporting the association is due to the fact that PNH is an orphan disease for the diagnosis of which there is no high index of suspicion. Diagnostic tools for the same are not available in the countries that have a heavy burden of malaria. However such cases provide an excellent opportunity to study the clinical picture of two different causes of Haemolysis occurring together. Such cases may also provide an opportunity to study the effects of antimalarial drugs on PNH and that of eculizumab on malaria.

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