Anemic crisis due to *Mycoplasma pneumoniae* complication in sickle cell patients

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Sickle cell disease (SCD), one of the most common inherited hemoglobinopathies, remains a major public health problem with its various manifestations and complications. Hyposplenism, even in the presence of splenomegaly makes the patient prone to many infections, one of which is *Mycoplasma pneumoniae* (*M. pneumoniae*), a well known etiological agent of acute chest syndrome in SCD. Here, we report 3 cases of anemic crisis in sicklers due to *M. pneumoniae* infection.

Clinical features of 3 known sicklers admitted to Aseer Central Hospital, Kingdom of Saudi Arabia, over 4 months were analyzed, and their major clinical manifestations were tabulated. The *M. pneumoniae* infection was confirmed by comparing immunoglobulin (Ig) G antibody titers between the acute and convalescent phase of the illness following standard methodology.[1] An immune adherence assay was used (Remel Inc., Kansas, USA), and a 4-fold rise in IgG titers was considered evidence of *M. pneumoniae* infection. In those patients with high standing IgG titers (IgG levels ≥1024), acute serum was analyzed for the presence of IgM antibodies with an enzyme immunoassay for *M. pneumoniae* (ImmunoWell [Gen Bio], San Diego, CA). A summary of the 3 patient's clinical, hematological, biochemical, and immunological data with treatment outcome are presented in **Table 1**.

Mycoplasma pneumoniae, which is known to produce mild or atypical pneumonia in young adults produces severe manifestations in SCD patients, as it is the most common causative agent for acute chest syndrome. The 3 patients in this report presented with an anemic crisis, and showed IgM mycoplasma antibody in their serum, which is a reliable indicator of recent infection.[1] Another striking feature is the low reticulocyte production index (RPI) improvement of which heralded the recovery. Acute hemolytic anemia can occur in <5% of patients with *M. pneumoniae* when the cold agglutinin titer is greater than 1:512.[2] In our patients, the cold agglutinin titer was never high enough to produce such typical hemolysis. However, the presence of cold agglutinins

Table 1 - Patient data, clinical features and laboratory investigations at the time of anemic crisis of 3 sickle cell patients.

Clinical features and laboratory investigations	Patient 1	Patient 2	Patient 3
Age (years) / gender	13/ F	20 / M	13 / F
Complaint	Fever, dizziness, and abdominal pain	Fever, confusion, and weakness	Fever, general pains, and weakness
History of similar episodes	3 times over the last 3 weeks	Once in the last week	No
Hepatosplenomegaly	Persistent	Reduced after the crisis	Not present
Drop of hemoglobin (g/dL)	9.7 to 6.4	7.3 to 2.7	10.3 to 6.4
Reticulocytes count, %	2.2	13	0.5
Erythrocytes sedimentation rate, mm/hr	130	50	70
Blood smear	Dimorphic anemia	Hemolytic anemia, clumping, and normoblastemia	Dimorphic anemia and LEA
Bilirubin (total/direct), mg/dl	1.6/0.8	3.2 / 0.9	2.9 / 0.1
Coomb's test	Positive	Positive	Negative
Cold agglutinins	Weak (+)	(++) (1:16)	Negative
Hemoglobin (Hb) electrophoresis %	Hb. A: 62 Hb. S: 38	Hb. A: 64 Hb. S: 36	Hb. A: 65 Hb. S: 35
Septic screen	Klebsiella sp. in urine C/S	Negative	Negative
Steroid therapy	Prednisolone	Hydrocortisone + prednisolone	Not used
After 2 days of therapy			
Hemoglobin g/dl	6.7	7.2	9.1
Retic %	16.5	16.5	18.4
RPI at admission-at crisis, and 6 days post therapy	3.4 to 0.53-3.3	2.1 to 0.92-2.6	0.84 to 0.22-5.5

ESR - erythrocytes sedimentation rate, RPI - reticulocyte production index, LEA - leuco-erythroblastic anemia

and positive Coombs test denotes some immune pathogenesis of anemia. It is not impossible to have hemolysis in cold hemagglutinin disease if there is impairment of C3b inactivator protein or production of IgM auto antibody with high thermal amplitude.[3] These will allow completion of complement cascade in visceral circulation, and produce severe extra vascular hemolysis. So this could be a possible pathogenesis in one of our patients who showed acute hemolytic episodes with enlargement of spleen (**Table 1**).

Immune mediated disorders of erythropoiesis can result in anemic crisis due to pure red cell aplasia, or ineffective erythropoiesis by humoral or immune mechanisms. Autoimmune hemolytic anemia (AIHA) with reticulocytopenia may present as a medical emergency for which prompt treatment with steroid and/or immunosuppressive therapy, along with careful transfusion are life saving measures. The reported prevalence of reticulocytopenia in AIHA varies widely from ~10-50% of cases, and are distributed between warm and cold antibody types primary and secondary cases.[4] Many such reports have demonstrated antibodies against reticulocytes or erythroblasts.[4] Reticulocytes may be selectively destroyed if antibodies are directed against antigen sites on these young red cells, thus giving rise to negativity in Coomb's test too, as observed in one of our patients (**Table 1**) who had a relatively mild disease.

All our patients were on folate supplement therapy and had normal mean corpuscular volume, and so folate deficiency is not a possible etiology. Atypical hyper hemolytic transfusion reaction in SCD has been well described in the literature, in which hemolysis of both transfused and autologous cells can occur. Reticulocytopenia also can be seen in this from increased adhesion and accelerated destruction of reticulocytes by hyperactive marophages.[5] One of our patients had recurrent episodes of acute hemolytic anemia with poly agglutinable red cell antibodies producing difficulty in cross matching. As elution techniques were not available, we could not characterize them, but our patients promptly responded to steroids and did not react to subsequent transfusions.

The 3 cases of recurrent anemic crisis due to *M. pneumoniae* infection among Saudi patients known to have SCD presented with symptoms of anemia, and did not respond to packed red cell transfusion. Presence of cold agglutinins, positive Coomb's test, and response to steroid therapy indicate an immune pathogenesis. The RPI observed in these patients along with erythroid hyperplasia or leucoerythroblastic reaction at the time of crisis, suggests that ineffective erythropoiesis due to antibodies directed against reticulocytes could be the possible pathogenesis.

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