PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA A RARE HAEMATOLOGICAL DISORDER – LITERATURE REVIEW AND CASE REPORT

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Abstract

A 68 years old fair complexion lady was presented with 2 months history of weakness several episodes of fever and multiple bruises in different parts of the body, admitted in a local private clinic of chittagong in 2003. On examination she had no organomegaly, lymphadenopathy or bone tenderness but had anaemia, petichiae in addition to skin bruises. In the laboratory investigations her haematology profile including blood film morphology and marrrow aspiration cytology was compatible with aplastic anaemia. Blood chemistry, chest skiagram, electrcardiogram and abdominal ultrasonogram revealed no abnormality but she noticed passage of high coloured urine in several times specially in the morning. But there was no other significant urinary findings in routine microscopy. Later on she goes abroad without receiving any specific treatment in Bangladesh except blood transfusion and other supportive drugs accordingly.There she was detected with PNH clone in addition to bone marrow aplasia and advised to receive immunosuppresive therapy either ATG or ALG followed by cyclosporine. She couldno't afford immunosuppresive therapy due to economic reason so she was treated with androgenic steroid along with sequential corticosteroid therapy for six months which gradually improved her blood count and became transfusion free.

Key words: paroxysmal nocturnal; haemoglobinuria; anti thymocyte globulin; anti lymphocyte globulin; bone marrow transplantation; phosphatidyl ionisitol glycan- A; decay acceleratig factor; membrane inhibitor reactive lysis; cluster differentiation antigen.

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Background

PNH is a rare acquired haematological marrow stem cell disorder seldom occours, possibly not yet reported in our country due to limited sophisticated diagnostic facilities.On the other hand BMT is the only curative option of treatment which is costly as well as has a significant morbidity and mortality. Currently a new approach of immunotherapy (Eculizumab) is reported that effectively reduces the haemolytic process which can provide an opportunity to receive the most definitive as well as curative option of BMT uneventfully by sparing the patient from blood transfusion support. So recent advancement of therapy and our experiences of androgenic steroid response in such an elderly lady prompted us to report this rare haematological disorder as well as highlight the clinical and diagnostic features of the disorder.

Introduction

Paroxysmal nocturnal haeoglobinuria- the term PNH is used for short, is an uncommon acquired clonal marrow stem cell disorder. It is characterized by variable degree of anaemia resulting from episodic haemolytic attack along with passes of dark coloured urine specially in the morning. It is also associated with febrile attack, bleeding menifestations and occasional abdominal pain due to neutropenia, thrombocytopenia and venous thrombosis respectivel[1-4]. The underlying pathophysiology of PNH is complement induced blood cell destruction particularly red blood cell due to lack of some proteins in their cell membrane that inhibit complement activation and prevent lysis[2-5]. These membrane protecting phosphatidylionisitol glycan class –A anchored proteins are deficient due to somatic mutation in PIG-A gene that unable to express this anchoring substance, phosphatidylionisitol glycan class-A in their cell membrane[6-7]. So diagnosis of PNH needs some sophisticated immunologic procedure(Flow cytometry) to detect these surface protein expression along with other routine and specialised haematologic investigations. The specific and curative option of treatment of PNH is allogenic BMT.But no other therapies can minimize the haemolytic process except recent advances of

immunotherapy(Eculizumab)[8-10]. Immunosuppresive therapy and use of androgenic steroid can only improve the erythropoeisis. Besides symptomatic supports like blood transfusion and antibacterials are also required time to time[11-12]. But recurrent blood transfusion may complicate the potentialy succesfull curative procedure of allogenic Bone marrow transplantation.

Case Report

Mrs "AB" is a 68 years old fair complexion non diabetic, normotensive bulky lady without having any sibs was presented with 2 months history of severe weakness, recurrent bouts of fever,skin bruises and petichial rash at multiple sites of the body. On examination she was found to be anaemic but anicteric had no organomegaly, lymphadenopathy or bone tenderness. She had no exposure to cytotoxic drugs, chemicals or any kind of infectious agents including hepatotrophic viruses. Her laboratory investigations revealed as in haematology :Hb%:8.4gm%, PCV:28.4%, RBC:3.43X1012/L, MCV:83.4fl, MCH: 27.4 pg, MCHC:32.9mg%, RDW: 16.6%,WBC; TC: 1.7X109/L,DC; N:30%,L:66%, M:04%, PLT: 09X109/L,Retics count:01%, blood film morphology : minimum anisopoikilocytosis in RBC. Marrow aspiration cytology and surgical biopsy: Hypocellular marrow in all of haemopoeitic cell line with increased number of lymphocytes and plasma cells, compatible with hypoplastic bone marrow failure .Blood chemistry; Total protein: 7.1gm% albumin:3.1 gm% globulin:4.0gm%, Billirubin: 0.4mg%, ALT: 84IU/L, AST: 49 IU/L,Alk. phosphatase:79 IU/L,uric acid:3.8mg%, LDH: 278U/ creatinine:0.9mg%BUN: 05mg% ,Random blood glucose: 147mg%,Electrolytes; Na:139 meq/L,K: 3.8 meq/L, Cl: 103meq/ L, HCO3:27 meq/L, Calcium: 9.4mg%, Phosphate :3.1mg%. Viral markers and direct coomb's test were found to be negative. Serum Epo level was increased ; >200IU/L. Urine: R/M/E: Only few RBC / HPF,haemosiderin was negative. Chest skiagram shows lower lobe consolidation of Lt. Lung. Immunhaematology detected partial loss of CD 55, CD 59, CD16 antigen –suggesting presence of PNH clone.From above findings her final diagnosis was Aplastic anaemia with PNH clone and pneumonic consolidation of Lt. lung.Besides symptomatic treatment she was advised for immunosuppresive therapy with ATG/ALG followed by cyclosporine. But she couldn't afford it due to economic reason. At last she was tried with marrow stimulant oxymetholone along with corticosteroids and subsequent follow up after six month she revealed dramatic improvement in her blood count and ultimately became transfusion free. She is still alive without any PNH event except disease of aging.

Discussion

PNH is a rare disorder with an annual incidence of 1/ 100,000 to 1/ million. However it is rarely heard in our country specially in our limited haematological set up. It can occour at any age and affects both male and female equally even rarely in children also[5,13-14]. PNH is not an inherited condition and cannot be passed from one person to another.There is no increased risk of occourence in family members. PNH is caused by the change (mutation) in a X-linked phophatidyl ionisitol glycan class-A (PIG-A) gene that causes the deficiency of phophatidyl ionisitol glycan class-A protein expression in the cell membrane. This PIG-A protein anchored some other complement inhibitory proteins that develop during life so that deficient PIG-A leads to deficiency of these essential proteins. The deficiency of these essential proteins CD55 (DAF) and CD59 (MIRL/Homologous restriction factor) thus fails to protect blood cell destruction from complement specially red cell (intravascular lysis) which results anaemia and other cytopenias. The mutation affects very earliest kind of blood cell in the bone marrow. the blood forming organ. This cell is known as haemopoeitic stem cell or Marrow "seed cell" because it has the ability to produce three kind of blood cells i.e red blood cells, platelets and white blood cells. The PNH abnormality is therefore found in three types of cell line. There is a close relation of aplastic anaemia conversion to acute leukaemia that occours in 5-15% of all cases[15-17].

In PNH the red blood cells produced from mutated stem cell are weak and thus destroyed more rapidly than normal specially at night in low PH condition when complement is activated and thereby episode (Paroxysm) of blood cell particularly red blood cell destruction occours. Patient passes dark (coffe /cocca-cola) colour urine in the morning that became clear through the day. As a result patient feels weak due to anaemia and mild abdominal discomfort to severe abdominal pain during the haemolytic episode.

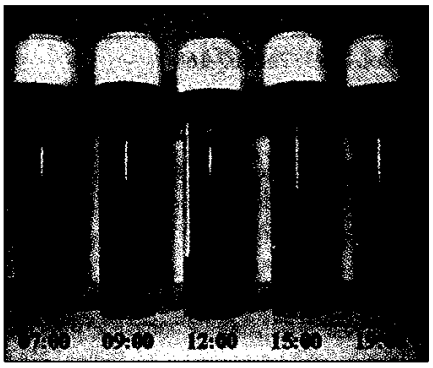

Fig 1 : Urine specimen of haemoglobinuria from 7-00 to 19-00 hours

The three major clinical problems associated with PNH are;

- The premature red cell destruction causing anaemia and passes of episodic dark colour
- urine specially in the morning that may leads to renal insufficiency[14].
- Reduced ability to produce blood cell in the marrow (hypoplastic/ aplastic) leads to anaemia, neutropenia and thrombocytopenia/ pancytopenia that causes features of anaemia, recurrent infection and bleeding menifestations respectively[6-7].
- Clots occouring in the vein ñ venous thrombosis[1-4].

The course of the PNH is very variable. In most cases PNH goes on for many years and patient gets used to living with the disease.Many patients lead an active life with little disruption as possible caused by their PNH, needs only haematological follow up.However complications can arise and the severely affected patients needs treatment intervention.

Diagnosis of PNH is usually done by complete blood count, reticulocyte count, blood film morphology study, bone marrow biopsy studies including iron stain and immunologic studies. Other secondary aetiologies of marrow aplasia like drugs, chemicals and industrial exposure and exposure to haematotrophic viruses also to be excluded. Sucrose haemolysis and complement mediated acid haemolysis (Hamís) tests are used popularly for diagnostic confirmation. But now a days flow cytometric analysis for PNH marker (CD55, CD59) and FCM quantification with fluorescent lebelled inactive toxin aerolysin (FLAER) has replaced these popular tests[18]. In the series of 78 cases of PNH by Zhao et. al Hamís was positive in 65.8% cases whereas CD59 and CD55 were found deficient in 100% cases.

The specific and only curative option of PNH treament is Bone marrow transplantation[19-20]. Other modalities are immunosuppresion with ATG /ALG/methyl prednisolone/cyclosporin-A, either alone or in combination with marrow stimulants, androgenic steroid like oxymetholone/nandrolone or human recombinant erythropoeitin.But none can minimize the underlying pathophysiologic haemolytic process except monoclonal antibody therapy that inhibits complement (C5). Recent advances of complement (C5) inhibition by monoclonal antibody (Eculizumab) therapy along with bone marrow stimulants show more promising result to lead an event free life[8-10]. It can spared blood transfusion support and thereby help to receive a more successful curative option marrow engraftment uneventfully in future.Besides BMT has a high morbidity as well as mortality though now a days these are overcome by more sophisticated measures yet it is also to costly and hardly affordable to our only limited number of patients in Bangladesh.

Conclusion

Bangladesh is a developing country. So the patients of such a rare disorder should have to manage more successfully as well as rationally and also look for the specific option of treatment. Yet to lead an eventfree and good healthful life patients also need to treat with blood transfusion which should be rationale. On the other hand to halt the haemolytic attack immunotherapy (C5 inhibitor) is the novel approach now a days that prevents anaemia. Use of erythropoeitin and other bone marrow stimulants like androgenic steroids also further augment the erythropoeisis and thereby minimize the requirement of blood transfusion and eventually patient became transfusion free. As a consequence it becomes easy and uneventful to receive the more successful as well as curative modality of PNH treatment, Bone marrow transplantation in future.

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