Paroxysmal nocturnal haemoglobinuria and its various manifestations
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INTRODUCTION
Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder resulting from a somatic mutation in the hematopoietic stem cell. It is characterized by intravascular hemolysis, cytopenias, frequent infections, bone marrow hypoplasia, and a high incidence of life-threatening venous thrombosis. An absent glycosylphosphatidylinositol (GPI)-anchored receptor prevents several proteins from binding to the erythrocyte membrane. These include the complement-regulatory proteins, CD55 and CD59, whose absence results in enhanced complement-mediated lysis. Patients present with anemia and hemoglobinuria.

CASE REPORT
A 24 year old Caucasian male was brought to the A &E with altered consciousness. He was feeling unwell for the past few days as per his girl friend. Background history showed a history of paroxysmal nocturnal haemoglobinuria [PNH] for which he was on treatment with warfarin folic acid, iron supplements and steroids for the past 1 year. History of thrombosis in mesenteric veins was present. He also had Budd Chiari syndrome had undergone TIPPS procedure and have a venous filter in his inferior venacava. On examination there was generalized purpura. He had low oxygen saturation, was hypotensive, tachypneic and tachycardic. The patient started desaturating and had to be intubated. Monitoring was done with pulse oxymeter, arterial BP, CVP and renal output monitoring. Hypotension was present which did not respond to fluids, so was started on Noradrenaline infusion. There was no renal output .CVP was low and did not increase with colloid infusions. Cyanosis started setting in even after ventilation with 100 % oxygen. ABG showed severe metabolic acidosis.

Lab reports showed severe thrombocytopenia, anemia, increased INR, hyperkalemia, hypocalcaemia and increased D-Dimers. Based on his previous history it was concluded that he was having a severe episode of haemolysis superimposed on severe infection. The clinical picture pointed towards meningococcal septicemia with waterhouse-friderichsen syndrome .The patient was given platelet infusions and hydrocortisone. Inspite of all the supportive measures, the patient died after 3 hours.

DISCUSSION
Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal chronic haemolytic anaemia in which intravascular haemolysis resulting from an intrinsic defect in the membrane of red cells which makes the red cells highly susceptible to complement. In the 1930’s Ham in the USA , and Dacie in the UK , developed the acidified serum test, which became the defining diagnostic test for PNH.

In contrast to all other haemolytic anemias due to an intrinsic red cell abnormality, PNH is an acquired rather than an inherited disorder. This fact, together with the finding that
normal cells co-exist in the patient's blood with those that are
hypsersensitive to complement, led some 35 years ago to the
working hypothesis that PNH arises through a somatic
mutation in a haemopoietic cell. 3

This disease has been referred to as the great impersonator
because of the variety of symptoms observed during the
initial manifestation and course of the disease. The clinical
syndrome can present in 3 types of symptoms including (1)
an acquired intracorpuscular hemolytic anemia due to the
abnormal susceptibility of the red cell membrane to the
hemolytic activity of complement; (2) thromboses in large
vessels, such as hepatic, abdominal, cerebral, and subdermal
veins, and (3) a deficiency in hematopoesis that may be
mild or severe, such as pancytopenia in aplastic anemia
state. The triad of hemolytic anemia, pancytopenia, and
thrombosis makes PNH a truly unique clinical syndrome.

There are varying reports regarding the onset of symptoms.
The range varies from 2 to 80 years, but it now understood
that the median age is around 40 years. Men and women are
affected equally, and no familial tendencies exist. A study
done shows that white American patients were younger with
significantly more classic symptoms of PNH including
thrombosis, hemoglobinuria, and infection, while Asian
patients were older with more marrow aplasia and a smaller
PNH clone. 4 There is an increased risk of infections in
patients with PNH due to aplastic bone marrow. The
generalized pancytopenia and splenic vein thrombosis put
the patient to an increased risk of capsulated organisms like
pneumococci, meningococci and other encapsulated bacteria.

There have been case reports suggesting that cerebral
thrombosis might be the first manifestation of PNH. 5, 7
Transjugular intrahepatic portosystemic shunt is done for
patients who come with Budd chiari syndrome which is a
very common occurrence in patients with PNH. 8 There are
an increased risk of thrombosis in mesenteric veins and also
the subdermal veins. Splenomegaly can be manifested by
splenic vein thrombosis and papilledema can be found in
cerebral thrombosis.

The intravascular haemolysis manifests as dark cola-colored
urine that is a manifestation of hemoglobinuria. The latter
may be confused with hematuria, and erroneous treatment
could be given for urosepsis. Hemosiderin nearly always is
present in the urine sediment and can accumulate in the
kidneys, which shows up on MRI or CT scans. Elevated
reticulocyte count and serum lactic acid dehydrogenase
(LDH) with a low serum haptoglobin in the absence of
hepatosplenomegaly are the hallmarks of intravascular
hemolysis. Bone marrow usually is markedly erythroid, with
decreased or absent iron stores, depending on how long the
patient has been losing iron in urine. Acute renal failure has
been documented in PNH. 9 Though rare purpura fulminans
is also seen. 10

Lab diagnosis involves demonstration of the presence of
RBCs that are exceptionally sensitive to the hemolytic action
of complement. The state-of-the-art laboratory test is to send
the patient's blood for flow cytometry to detect CD59
(MIRL), a glycoprotein, and CD55 (DAF) in regulation of
complement action. Absence or reduced expression of both
CD59 and CD55 on PNH red cells is diagnostic. 11 A recent
study identified a novel autosomal recessively inherited form
of GPI-deficiency involving a mutation in a promoter
component of the pig-m gene and characterized by a
thrombotic tendency and seizures. In both these
developments, flow cytometry played a critical role. In the
first instance, in monitoring direct response to a new
therapeutic agent; second, in demonstrating the
phenotypic/genotypic link in a new form of GPI deficiency. 12

Hepatic vein thrombosis is detected with a routine
technetium Tc 99m colloid scan of the liver and spleen. This
often reveals diminished function in all portions of the liver
except the caudate lobe, which is spared because it is drained
by the inferior vena cava rather than the hepatic vein. An
MRI or ultrasound can demonstrate the cessation of flow
through the hepatic vein or by injecting or using a dye to
demonstrate thrombus in the vein. MRI with contrast may
demonstrate sagittal vein thrombosis. 13

Treatment includes folic acid 5mg/day in view of increased
rate of erythropoiesis.

Assess iron stores using transferrin saturation index (TSI):
Give oral ferrous sulfate if <20%. (Ferritin is acute-phase
reactant and can be misleading.). Determine steady state Hb
levels after correction for iron deficiency. Transfuse packed
RBC (WBC depleted by filter) when appropriate. Washing
red cells is no longer necessary, and irradiated blood
products is recommended for future.

Modulation of complement is controlled poorly by high
doses of glucocorticoids. The usual adult dose of prednisone
is 20-40 mg/d (0.3-0.6 mg/kg/d) given daily during
hemolysis and changed to alternate days during remission. A
new anticomplement agent, eculizumab, is a humanized
monoclonal antibody against terminal protein C5; it has
recently been shown to be highly effective in reducing intravascular hemolysis.\textsuperscript{14,15} Stimulation of erythropoiesis using androgenic hormones has been successful in patients with moderate decrease in red cell production. This has been replaced mainly by using recombinant erythropoietin therapy.

If bone marrow transplantation can be done it is the treatment of choice for cases of aplastic anemias.

In our case the patient presented with purpura fulminans with symptoms and signs of intravascular haemolysis, thrombocytopenia, DIC and signs of sepsis. Purpura fulminans is a manifestation of severe infections like meningococcal infections, toxic shock syndrome and drug reactions\textsuperscript{16,17}. There is an increased incidence of infections in patients with PNH\textsuperscript{18} Because of overlap of many of the symptoms, it might be differentiate the primary cause of purpura fulminans. We concluded that the patient had meningococcal infection leading to picture of DIC, resistant hypotension superimposed on PNH, which was later established by laboratory results. New studies have been done regarding the use of activated protein C in treatment of purpura fulminans due to infections\textsuperscript{19} but its use is not fully conclusive. No studies have proved conclusively the use of haemodialysis in treatment of acute episodes of PNH. This case highlights the different manifestations of a patient with PNH due to decreased immunity.

References

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