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Black Mornings, Yellow Sunsets

KEYWORDS: PNH, PIG-A gene, haemoglobinuria, thrombosis, hemolytic anemia.

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ABSTRACT *Paroxysmal Nocturnal Hemoglobinuria (PNH) is an acquired clonal hematopoietic (one or several) stem cell disorder, where there is mutation in somatic PIG-A gene, deficient glycosyl phosphatidylinositol- anchored proteins (GPA-APs), which in turn results in deficiency in GPI- anchored complement proteins CD55, CD59 resulting in intravascular haemolysis.*

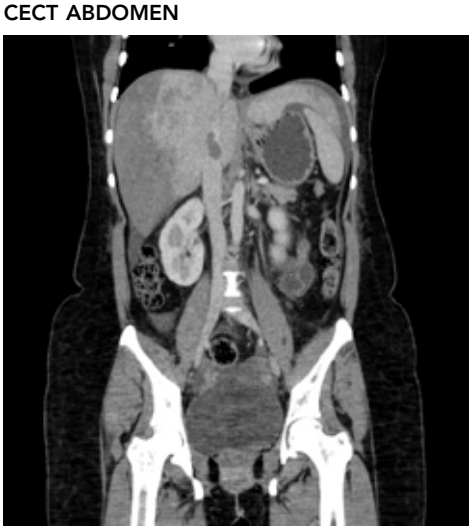
CASE REPORT:

We had a 21 year old female patient, who presented with a 1 month history of jaundice, passing dark-colored urine, fever on and off, 15 days history of diffuse abdominal pain, 1 day history of left-sided headache associated with sudden onset of blurring of vision in right eye.

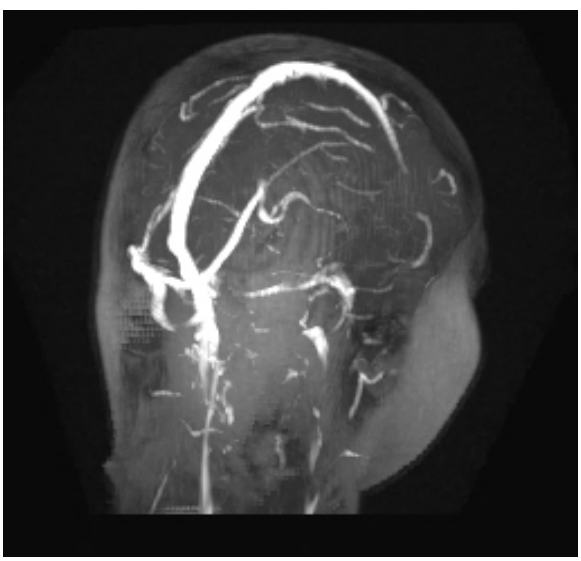
On examination, vitals were stable, pallor, icterus present. On systemic examination, abdomen was soft, diffuse tenderness and hepatomegaly present; fundus showed superficial hemorrhage, whilst other systems were normal.

On investigating, hemoglobin was low with 5.2 g%, platelets were 56,000 cells/cu.mm, ESR was 55 mm/Hr, peripheral smear showed normocytic normochromic picture with adequate platelets; liver function tests showed altered enzymes of SGOT 202U/L; SGPT:135 U/L; LDH:1849. Autoimmune work-up; ANA, dsDNA, APLA were negative. Also thyroid profile, was normal, stool for occult blood, direct Coomb's test, viral markers were negative. Also serum iron, ferritin, TIBC was normal. Serum homocysteine was normal: 5 µmol/L. Ultrasound abdomen done showed hepatomegaly with coarse echotexture, minimal ascites and thrombosis involving intrahepatic segment of IVC and hepatic confluence. Further, CECT abdomen done was suggestive of thrombosis involving intrahepatic segment of IVC and hepatic confluence; indicating of possible Budd-Chiari syndrome.

CECT ABDOMEN



MRI BRAIN WITH VENOGRAM



MRI Brain with Venogram was suggestive of sub-acute bleed of size 3.5 x 2.5cm in left occipital lobe, absent flow noted in left transverse, sigmoid sinuses and upper jugular vein.

Further, bone marrow aspiration and biopsy also was done which was suggestive of reactive marrow, dyserythropoiesis, megaloblastic maturation with binucleate forms, and all stage of maturation with giant metamyelocytes. In view of hemolysis plus unusual sites of thrombosis and bicytopenia with raised LDH, PNH was suspected. Flowcytometry was done, which showed PNH clone, with decreased percent of CD59, CD55-47% and 56.7% respectively.

TREATMENT:

We managed the patient with low molecular weight heparin 0.6ml subcutaneously, BD; overlapped with oral anticoagulation. Also 3 unit of packed cell was transfused. Tablet Danazol 200mg was initiated on BD basis, Folic acid

Also HLA typing was done for bone marrow transplantation which is the definitive treatment, but no match was found

DISCUSSION:

PNH is a clonal hematopoietic stem cell disorder that man-

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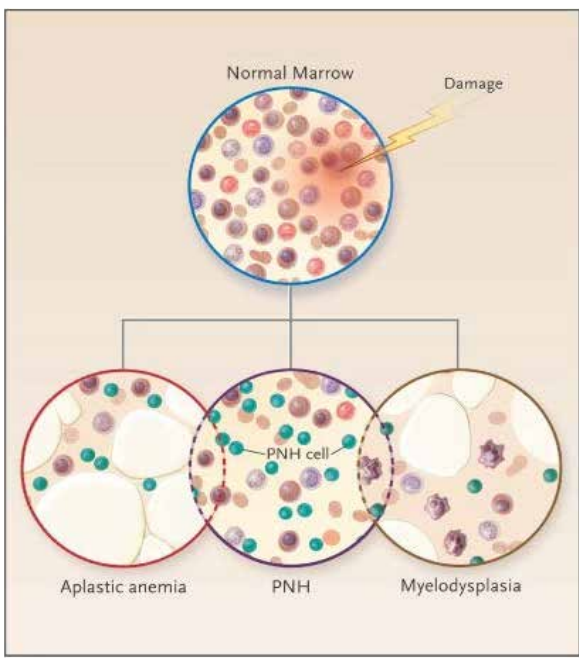
ifests with a triad of hemolytic anemia, bone marrow failure and unusual sites of thrombosis. The absence of 2 GPI- anchored proteins, CD55 and CD59, leads to uncontrolled complement activation that accounts for PNH features[1]. The pathogenesis is inability to produce the glycosyl phosphatidylinositol (GPI) anchor due to an acquired somatic cell mutation in the PIG-A gene. In all patients with PNH, cells partially or completely lacking GPI-linked proteins may be found among red cells[3]

CD59, also called membrane inhibitor of reactive lysis, is partially or completely missing from the hematopoietic cells

CD55 (decay accelerating factor), resulting in an increased sensitivity of the affected cells to the action of complement



Classification[2]:

- Classic PNH
- PNH in setting of another bone marrow
- Subclinical PNH

The diagnosis is based on

(a) Evidence of acquired haemolysis, specifically with a negative direct(Coombs) test

(b) Intravascular hemolysis (eg, hemoglobinemia,elevation of plasma lactate dehydrogenase levels)

(c) Venous thrombosis, particularly of the abdominal or cerebral veins (eg, Budd-Chiari syndrome, mesenteric or portal vein thrombosis, thrombosis of cerebral veins);(d)Absence of GPI linked proteins as demonstrated by flowcytometry.

CONCLUSION:

PNH is a very rare disorder (1 to 10 cases per million)[4]. Improved knowledge of the molecular and cellular underpinnings of PNH over the last 2 decades has resulted in greater understanding of the biology and natural history of PNH. Recent studies with the monoclonal antibody, Eculizumab, demonstrate that terminal complement inhibition controls most of the symptoms and life-threatening complications of PNH; however bone marrow transplant remains the only cure.

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