EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology Tutorial

Self-assessment Case – Session [2]

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Introduction

A 30-year-old man from eastern Uttar Pradesh presented in june 2017 with:

- Exertional breathlessness x1 year
- Weakness/lethargy x 1 year
- Cola coloured urine X 1 month
- H/O 3 units PRBC transfusion
- No family history of anemia/jaundice, No h/o drug intake
- O/E- Pallor+, Mild icterus, No lymphadenopathy or organomegaly

Laboratory Workup

- FBC showed
  - WBC 7.4 x 10^9/l
  - RBC 5.3 x 10^{12}/l
  - Hb 57 g/l
  - Hct 0.36
  - MCV 117.6 fl
  - MCH 27.7 pg
  - MCHC 32 g/l
  - Platelet count 182 x 10^9/l

  - Peripheral smear : Microcytic RBC , Few macrocytes , Polychromatophils
  - Reticulocyte count: 15%

Q1) Based on the blood count , smear and urine findings what is the most likely explanation of this anemia?

1. Megaloblastic anemia
2. Cold agglutinin disease (CAD)
3. Paroxysmal Nocturnal Hemoglobinuria (PNH)
4. Paroxysmal Cold Hemoglobinuria (PCH)
5. G6PD deficiency

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2.31 Based on the blood count , smear and urine findings what is the most likely explanation of this anemia?

ⓘ Start presenting to display the poll results on this slide.

Q-2 You would like to perform all of the following tests except?

1. Serum Vitamin B12 levels
2. G6PD levels
3. D-L antibody test
4. Coombs test
5. Flowcytometry for PNH Clone

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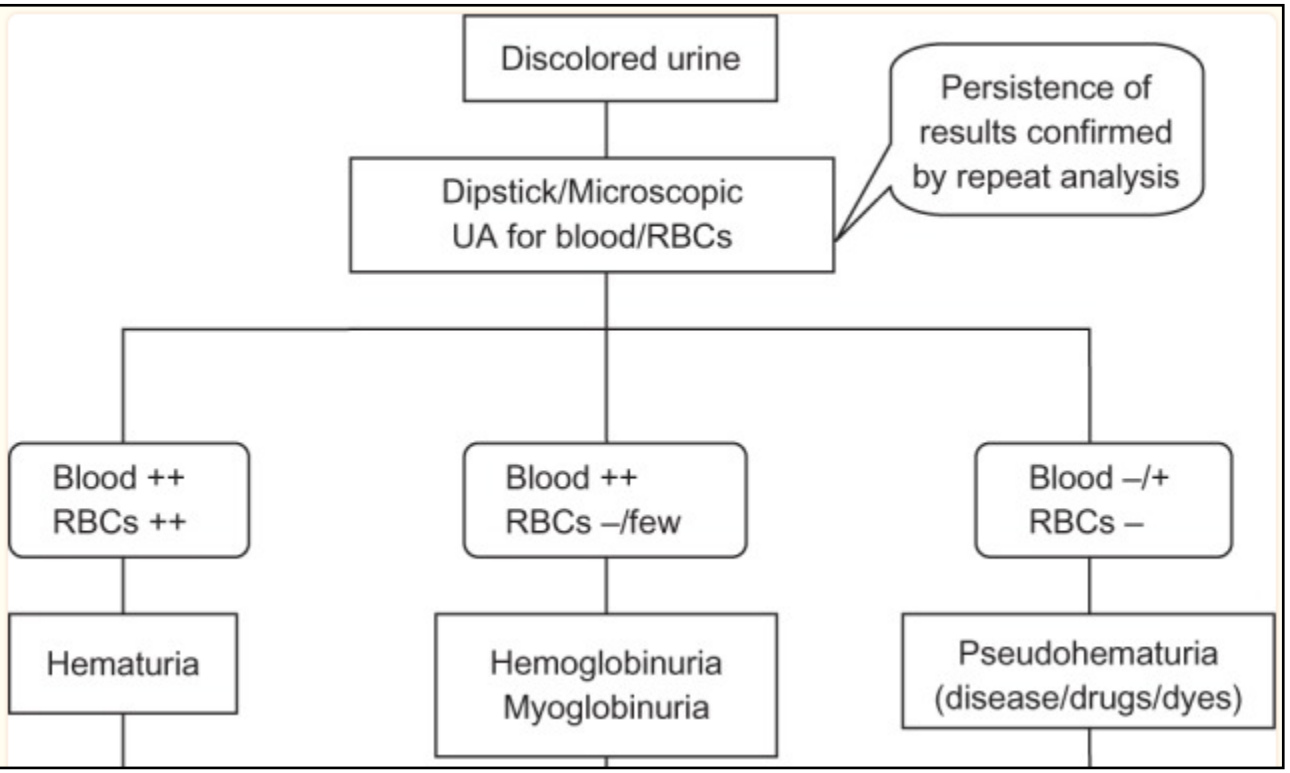
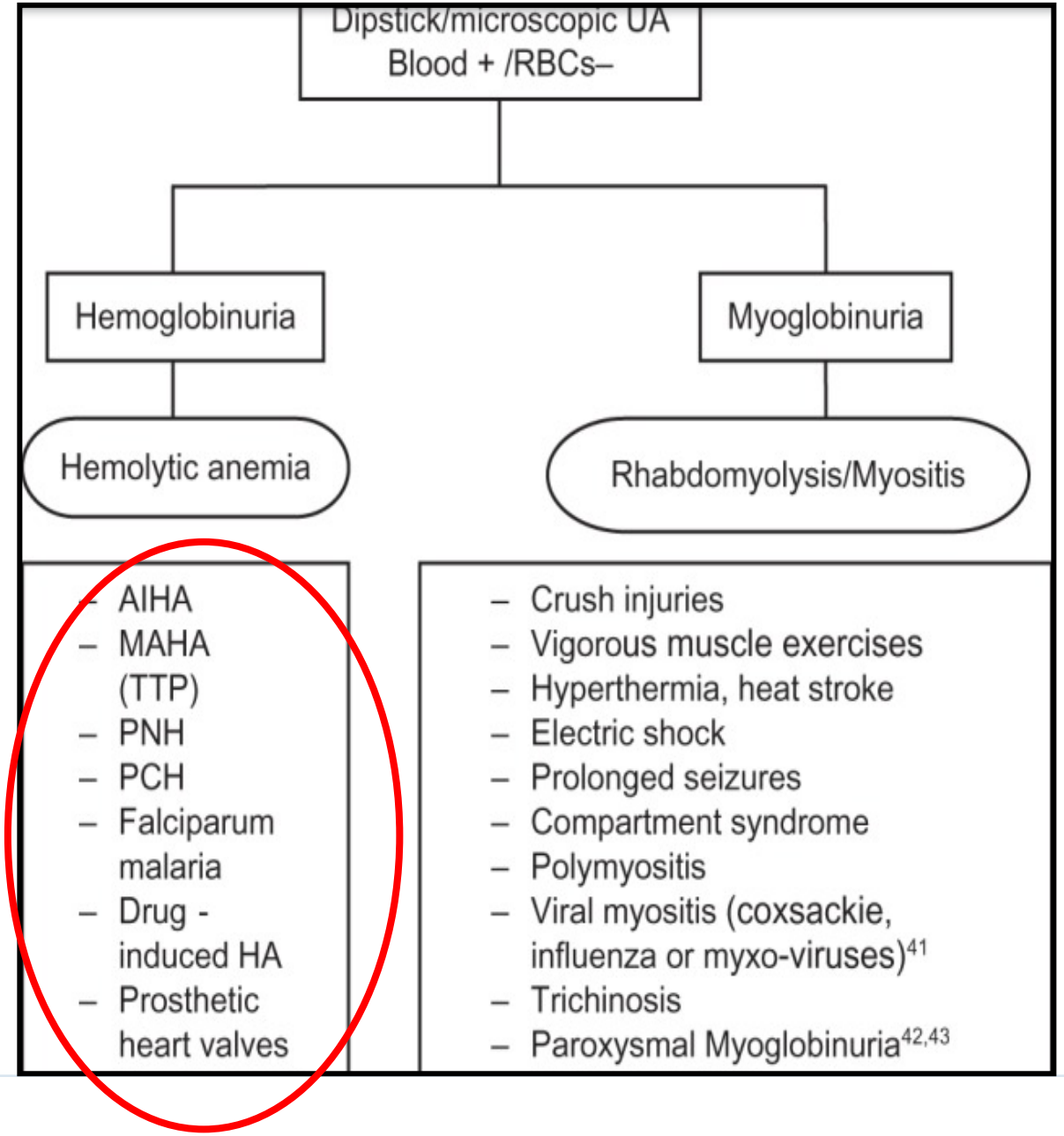
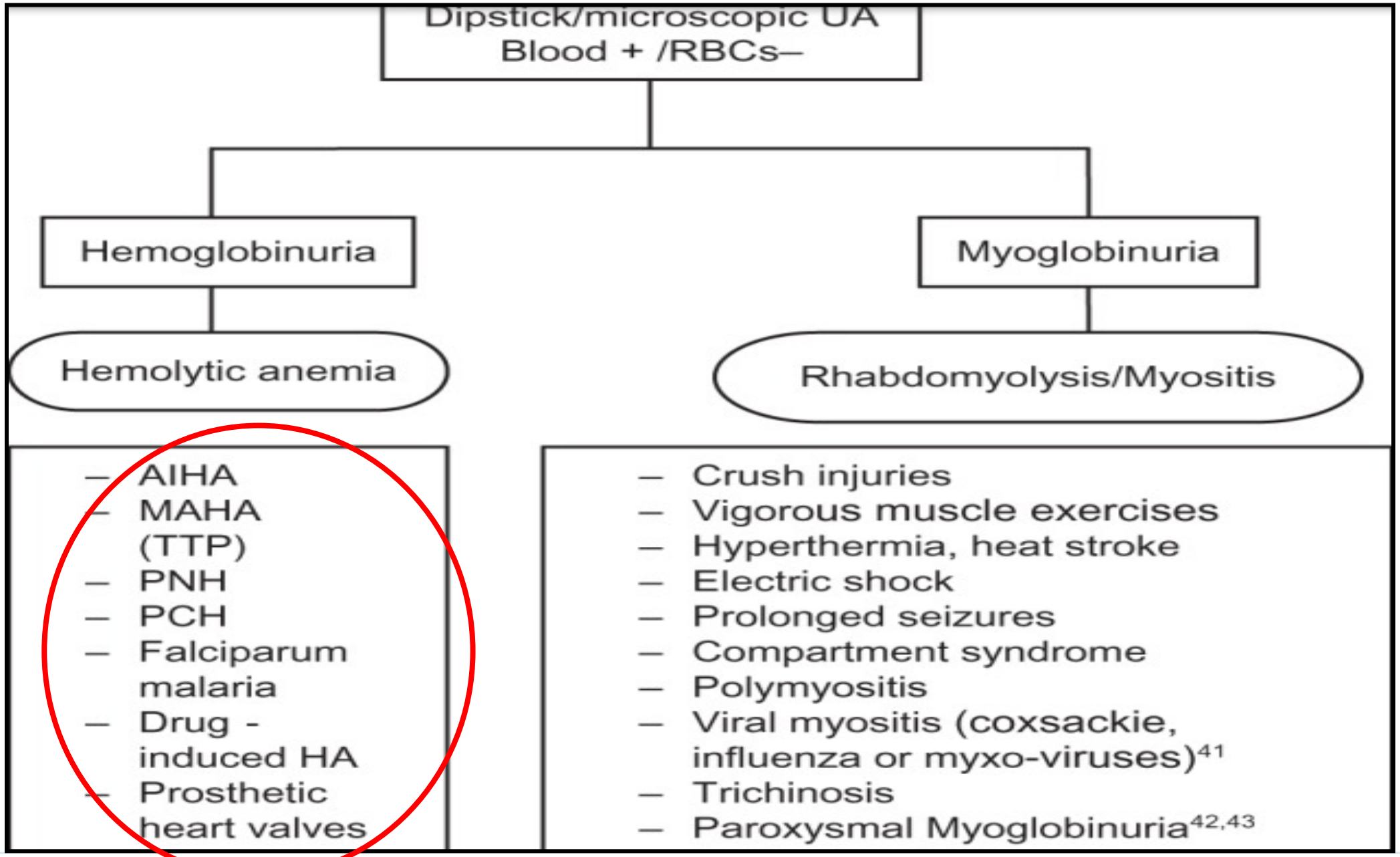
2.32 You would like to perform all of the following tests except?

ⓘ Start presenting to display the poll results on this slide.


Discolored urine
Persistence of results confirmed by repeat analysis
Dipstick/Microscopic UA for blood/RBCs
Blood ++ RBCs ++
Blood ++ RBCs –/few
Blood –/+ RBCs –
Hematuria
Hemoglobinuria Myoglobinuria
Pseudohematuria (disease/drugs/dyes)


Dipstick/microscopic UA
Blood + /RBCs–
Hemoglobinuria
Myoglobinuria
Hemolytic anemia
Rhabdomyolysis/Myositis
– AIHA
– MAHA (TTP)
– PNH
– PCH
– Falciparum malaria
– Drug - induced HA
– Prosthetic heart valves
– Crush injuries
– Vigorous muscle exercises
– Hyperthermia, heat stroke
– Electric shock
– Prolonged seizures
– Compartment syndrome
– Polymyositis
– Viral myositis (coxsackie, influenza or myxo-viruses)41
– Trichinosis
– Paroxysmal Myoglobinuria42,43



Prashanth V. Clinical Medicine Insights: Blood Disorders 2013:6 7–17

Further tests

1. Serum LDH – 1683 IU/L (140-280 IU/L)
2. Serum Haptoglobin: 15 mg/dl (40-200 mg/dl)
3. Urine: Hemoglobinuria+
4. Direct Coombs test- Negative
5. Serum B12 levels- 389 (160-950 pg/ml)
6. G6PD levels-12 units/gm of Hb (8.6-18.6 units/gm of Hb)
7. PNH by FLAER- CD55 & CD59 deficiency -15% , Monocytes CD14-35%, Granulocyte CD24 -67%
8. Serum ferritin – 15 (24-336mg/ml)

DIAGNOSIS

- Paroxysmal Nocturnal Hemoglobinuria (Hemolytic PNH)
- Iron Deficiency

Q-3 What % of patients with PNH present with hemoglobinuria?

- A- 30%
- B- 50%
- C- 75%
- D – 100%
- E - 60%

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2.33 What % of patients with PNH present with hemoglobinuria?

ⓘ Start presenting to display the poll results on this slide.

Q-4 Regarding PNH which statement do you think is most appropriate?

1. Acquired non-clonal hematopoietic disorder
2. The incidence of venous thrombosis is ~10-40%
3. Prophylactic anticoagulation is effective in prevention of venous thrombosis in classical PNH
4. Most common cause of mortality is transformation to leukemia
5. Iron deficiency is uncommon in Classical PNH

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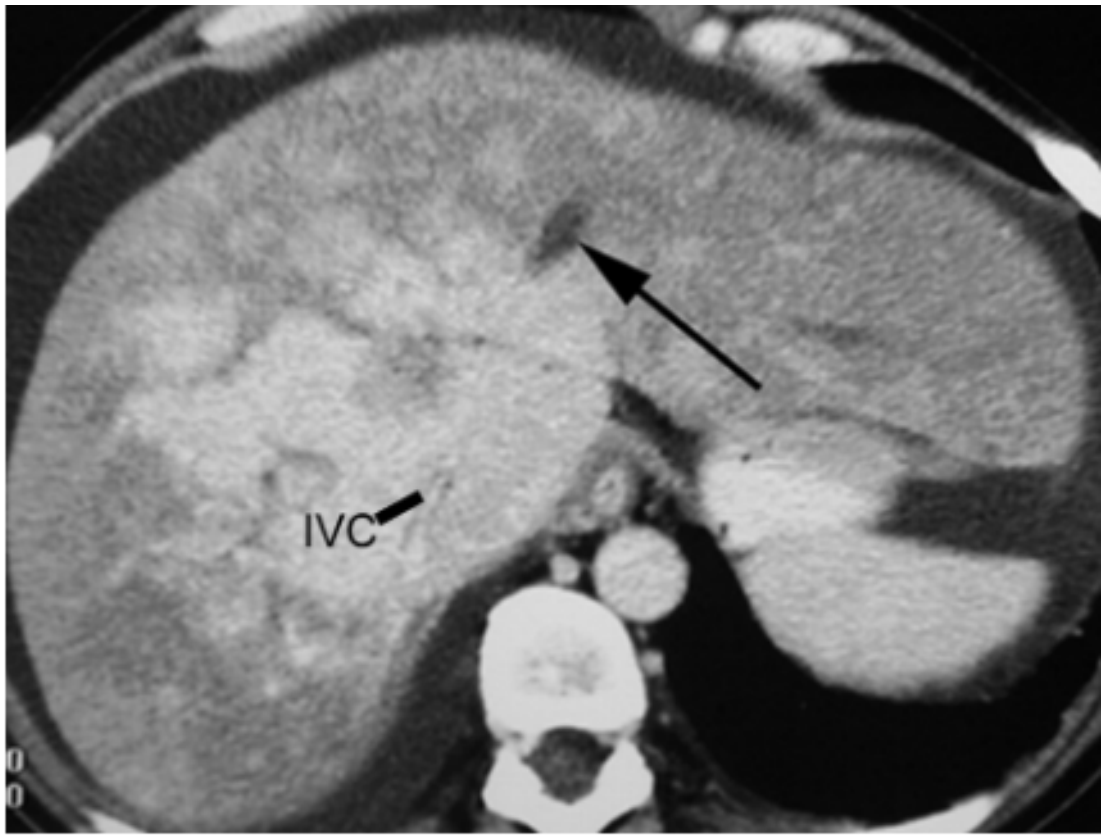
2.34 Regarding PNH which statement do you think is most appropriate?

ⓘ Start presenting to display the poll results on this slide.

Patient was started on

- Steroids Prednisolone 1 mg/kg BW
- Tab Folic acid 5 mg once a day
- Tab Ferrous ascorbate 1 tab twice a day

- He presented with acute onset right upper quadrant abdominal pain, and abdominal distension after 1 month
- CT Abdomen showed



CECT abdomen obtained during portal phase
Intense enhancement of Caudate lobe
IVC is compressed by enhanced caudate lobe
Thrombosis of left hepatic vein (arrow)

Brancatelli G et al. Budd Chiari Syndrome: Spectrum of Imaging Findings .AJR 2007; 188:W168–W1760361–803X/07/1882–W168

Q-5 In a case presenting with thrombosis, which condition we should test for underlying PNH?

1. Young Patients
2. Thrombosis at unusual site
3. Have evidence of hemolysis
4. Have any cytopenias
5. All of the above

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2.35 In a case presenting with thrombosis, which condition we should test for underlying PNH?

ⓘ Start presenting to display the poll results on this slide.

Q6) FDA has approved many drugs for PNH. Choose the incorrect option ?

1. Eculizumab is a monoclonal antibody and targets C5 can be given once in 2 weeks
2. Ravulizumab acts by inhibition of terminal membrane attack complex (MAC) formation and can be given once in 8 weeks
3. Iptacopan is an oral Factor B inhibitor that acts proximally in the alternative complement pathway of the immune system
4. Pegcetacoplan injection is the first PNH treatment that binds to compliment protein C3
5. Combination of pozelimab and cemdisiran is being evaluated in clinical trials and they Inhibit early complement pathway

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2.36 FDA has approved many drugs for PNH. Choose the incorrect option ?

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Feedback

Q1 The classic manifestation of paroxysmal nocturnal hemoglobinuria (PNH) is dark urine during the night with partial clearing during the day. However, hemoglobinuria may occur every day in severe cases; more frequently, it occurs in episodes lasting 3-10 days; and in some cases, it does not occur at all.

Q2 D-L antibody test is done for confirmation of PCH. PCH is typically found in children post viral infections or malinancy and typically occurs during winters with rapid onset hemoglobinuria.

Q-3 Not all patients have hemoglobinuria at the time of presentation. Only 30% pateints present with hemoglobinuria.

Q4 About 30-40% of patients of European origin have serious thrombosis at some time; for unexplained reasons, only 5-10% of patients of East Asian (Chinese, Japanese, and Thai) or Mexican origin develop this complication. [1,2]

Q5 Recommendations would be to consider testing for PNH by flow cytometry in those patients with unexplained thrombosis and those who: [3]

1. are young,
2. have a thrombosis in an unusual site (eg, intraabdominal veins, cerebral veins, dermal veins),
3. have evidence of hemolysis, or
4. have any cytopenia.

1.Socie G, et al. *Lancet*. 1996 Aug 31. 348(9027):573-7.
2.Nishimura J, et al. *Medicine (Baltimore)*. 2004 May. 83(3):193-207.
3. Hill A.Blood First Edition paper, April 22, 2013; DOI 10.1182/blood-2012-09-

- Q6 Pozelimab and cemdisiran are investigational agents with a subcutaneous (SC) maintenance regimen that may be self-administered; both inhibit terminal complement through complementary mechanisms of action. Pozelimab is a fully human monoclonal antibody inhibitor of C5, while cemdisiran is an N-acetylgalactosamine-conjugated small interfering RNA that suppresses liver production of C5 [4]

4. R.Kelly. Hemasphere. 2023 Aug; 7(Suppl): e6873083

Discussion

- PNH is one of the important causes of acquired hemolytic anemia
- It is an acquired hematopoietic stem cell disorders which occurs due to mutation in PIG A gene.
- This leads to absence of Glycosylphosphadtidylinositol(GPI) anchors and makes RBCs susceptible to hemolysis by terminal complement cascade (MAC C5-9)
- PNH is characterized by hemolytic anemia , hemoglobinuia, high tendency of thrombosis (venous> arterial) and progression to BM failure (Aplastic anemia/MDS)
- Thrombosis is the most common cause of PNH related mortality (40-60%)
- C5 inhibitors (Eculizumab/Ravulizumab) lead to accumulation of proximal complement C3b which coats the RBC and hemolysis occurs in Liver by Kupffer cells

PIG A gene- phosphatidylinositol glycan Class A gene

Suggested Readings

- Luzzatto L, Gianfaldoni G, Notaro R. Management of paroxysmal nocturnal haemoglobinuria: a personal view. Br J Haematol. 2011;153(6):709-720.
- Anita Hill, Richard J. Kelly, and Peter Hillmen. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;121(25):4985-4996)
- Broadsky R A . How I treat Paroxysmal Nocturnal Hemoglobinuria.Blood. 2021;137(10):1304-1309)

THANK YOU