ESIM Winter School Riga 2016

Quentin BODARD
Internal medicine, resident, France

Observation

- June 2015: female, 24 years old, student and vegan.
  - Progressive dyspnea in practicing sport since January
  - Emergency department admission for fatigue and severe dyspnea

- Medical history: appendectomy, no familial disease history
- Treatment: oral contraception

- Examination: BP: 106/60 mmHg HR: 100 bpm/min Sat: 99 % AA T: 37,2 °C
  Weight: 60 kg Length: 1,75 m BMI: 19 (no weight loose)
  Fatigue, pale skin, tachycardia, dyspnea (NYHA IV)
  Normal cardiopulmonary examination
  No pain, no other symptom
  ECG: sinusal tachycardia

- Blood analysis:
  - **Hb: 2,6 g/dl (>12)** MCV: 130 fl (80-100) reticulocytes: 55 G/l (70-120)
  - **PNN: 1,1 g/l (>1,5)**
  - **Platelets: 13 G/l (150-300**)
  - Haptoglobin: <0,10 g/l (0.30-2.00) Bilirubin: 21 µmol/l (2-18) LDH: 1300 UI/l (135-250)

Observation (2)

- Deep macrocytic and hemolytic anemia
- Pancytopenia

Hypothesis and explorations?

Hypothesis

- Hemolytic anemia: extra corpuscular? (4)
  - Mechanic: Microangiopathic hemolytic anemia (TTP, HUS, HELLPS, cancer)
  - Auto immune: red blood cell antibodies (hot or cold)
  - Toxic: treatment or exposition
  - Infection: viral infection, malaria
- Hemolytic anemia: corpuscular? (6)
  - Enzymatic deficit: G6PD or pyruvate kinase
  - Hemoglobin anomalies: thalassemia or sickle cell anemia
  - Membranous anomalies: spherocytosis or Paroxysmal Nocturnal Hemoglobinuria
- Nutritional deficiency

Hypothesis

- **Pancytopenia: Aplastic anemia** (11)
  - Drugs: ATB, NSAID, anti thyroid, chemotherapy, neuroleptic, …
  - Viral infection: parvovirus B19, HIV, post hepatitis, EBV, Dengue fever, …
  - Toxic: Benzene, insecticides, …
  - Pregnancy
  - Sequestration: splenomegaly
  - Nutritional deficiencies: copper or B9/B12 vitamins
  - Auto immune: Systemic Lupus Erythematosus (SLE), rheumatoid polyarthritis, …
  - Macrophage activation syndrome (MAS)
  - Paroxysmal nocturnal hemoglobinuria (PNH)
  - Hypoplastic myelodysplastic syndrome (MDS)
  - Idiopathic aplastic anemia

- **Pancytopenia: Marrow space infiltrating** (5)
  - Acutes leukemias
  - Lymphomas and multiple myeloma
  - Metastatics carcinomas
  - Fibrotics diseases

Weinzierl and Arber, *Am J Clin Pathol,* 2013

Diagnosis

- TSHus: 1.82mUI/l (N:0.4-4.0)
- Creatinine: 58µmol/l (N: 50-100)
- Schyzocytes: none
- COOMBS test: negative

- B12 vitamin: 67pmol/l (N:144-489)
- B9 vitamin: 20.7nmol/l (N: 11-34)
- Ferritin: 79µg/l (20-204)

- Myélogram: megaloblastic anemia

- **intra medullar hemolysis** and **megaloblastic anemia** by **vitamin deficiency**
- Due to **a strict vegan diet since childhood**
- **B12 vitamin** and **iron supplementations, red blood cell transfusions**

Diagnosis (2)

- July 2015:
  MCV: 98fl (80-100) Hb: 5,5g/dl (>12) Haptoglobin: <0,10 g/l (0.30-2.00)
  PNN: 510/mm3 (>1500) P: 24G/l (150-450),
  B12: 320 pmol/l (144-489**) B9: >45nmol/l** (11-34) **Ferritin: 1439 (20-204)**

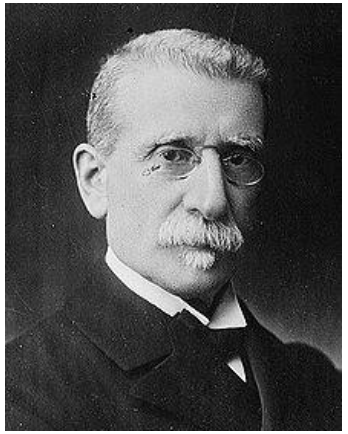
- Myelogram: erythroblastic hyperplasia, dyserythropoiese
- Bone marrow biopsy: anaplastic anemia without infiltrating

- **Paroxystic Nocturnal Hemoglobinuria** (PNH) clone at **Flow Cytometry**

- No thrombosis history
- Intra medullar hemolysis
- **Severe anaplastic anemia** (CAMITTA criteria)

- **Indication** to an **allogenic bone marrow transplantation (BMT)**
- **No indication** to **ECULIZUMAB**

PNH



- First described by **Marchiafava** in 1911 and **Micheli** in 1931

- Clonal hematopoietic stem cell disorder by a **genetic mutation of PIG-A**
  - **deficiency of GPI** that anchors >150 different proteins to the cell surface
  - with **complement inhibitory proteins** CD55 (DAF) and CD59 (MIRL)

- Diagnosis is made by **peripheral blood flow cytometry**

- **Hemolytic anemia**, **bone marrow failure** and **thrombosis**
  - Poor survival was associated with the occurrence of thrombosis as a complication
  - Better survival was shown for patient with the aplastic anemia type

Brodsky, BLOOD, 2014

PNH – Complications

Table 2. Clinical course and complications in the global population, N = 454

Complications	n/N (%)	10-year cumulative incidence rate, % (95% CI)
Bicytopenia or pancytopenia	36/231 (atrisk)§	19.2 (12.9-25.2)
Recurrent abdominal pain crisis	138/451 (30.2)	NA
Infections*	185/453 (40.8)	NA
Thrombosis	116/454‖	30.7 (25.4-35.9)¶
Budd-Chiari syndrome	49 (43)	
Central nervous system	35 (31)	
Limbs	31 (27)	
Other sites	29 (25)	
Myelodysplastic syndrome†	21/454	5.2 (2.9%-7.6%)
Acute leukemia†	8/454	2.4 (0.7%-4.0%)
Deaths‡	96/454	
Central nervous system (SCN) vascular complications	23	NA
Infectious diseases	23	NA
Budd-Chiari syndrome	21	NA
Malignant disorders	9	NA
Other causes	17	NA

Peffault de Latour, BLOOD, 2008

PNH - Treatment

- **Anti C5 monoclonal antibody: ECULIZUMAB**
  - Intravenous 600mg/week during 4 wks then 900mg/2 wks
  - Reduce 40% of transfusion needed
  - Reduce 85% of thrombosis

Hillmen, NEJM, 2006
Hillmen, BLOOD 2007
Brosky, BLOOD, 2008

- **allogeneic bone marrow transplantation (BMT):**
  - If severe aplastic anemia or severe recurrent hemolysis and thrombosis

Kawahara, Am J Haematol, 1992
Saso, Br J Haematol, 1999

- **Long term anticoagulation**: only if thrombosis history

Conclusion

- **Vitamin B12 deficiency can induce**:
  - severe anaplastic anemia

  AND
  - intramedullar hemolysis

- **Hemolytic anemia**, **central pancytopenia** and **atypical venous thrombosis** may lead to search **PNH clone** by **flow cytometry**

- **Anti C5: ECULIZUMAB** and **BMT** are major treatments in **PNH**