ACQUIRED HEMOLYTIC ANAEMIAS

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Introduction

• Normal red cell life span is 120 days after which senile cells are removed by the bone marrow and splenic macrophages.

• About 1% of red blood cells are broken down daily.

• Normally with an increase in red cell break down, there is increased Bone Marrow compensation.

• But in haemolytic conditions, the rate of red cell break down is increased
Introduction

• It leads to a reduced red cell survival.

• Anaemia occurs when the bone marrow is unable to compensate for the shortened life span of the red blood cells will manifest when the life span of the red cell is less than 20 days.

• In acquired haemolytic anaemia, the destruction of the red cells is not due to inherited membrane abnormalities or inherited disorders of the haemoglobin synthesis.
Causes of Acquired haemolytic anaemia

1. Immune

2. Non Immune: Mechanical
   - Infections
   - Toxins and Drugs
   - Others
Immune Haemolytic Anaemia

- These are classified into three groups
- Alloimmune haemolytic anaemia
- Autoimmune haemolytic anaemia
- Drug induced haemolytic anaemia
Immune Haemolytic Anaemia

- Alloimmune haemolytic anaemia: can be caused by
  1. Transfusion of incompatible blood
  2. Haemolytic disease of the foetus and new born
Immune Haemolytic Anaemia

- Autoimmune haemolytic anaemia can be classified based on either the aetiology or the pathogenesis

- Aetiologic classification includes

  1. Idiopathic (cause unknown)

  2. Secondary to B cell lymphoma, Chronic Lymphocytic Leukaemia, Immunodeficiency state, autoimmune states, viruses and mycoplasma
Immune Haemolytic Anaemia

- Pathogenic classification:
  1. Warm reactive antibody mediated
  2. Cold reactive antibody mediated
  3. Cold hemagglutinin disease
  4. Paroxysmal cold hemoglobinuria
- There is a point of unification between both classifications
- We shall focus on the later classification
Autoimmune Haemolytic Anaemia (AIHA)

- Autoimmune Haemolytic Anaemia is caused by attachment of antibodies to antigens present on red cell membrane.

- The rate and site of haemolysis depends on the type of antibody and its ability to fix complement.

- They are named warm or cold antibodies based on the optimal temperature at which they bind to the red cell membrane.
Autoimmune Haemolytic Anaemia (AIHA)

- Thee antibodies are against self antigens and are caused by deregulation of the immune system with increase in auto reactive B lymphocytes

- The antigens are red cell antigens
Autoimmune Haemolytic Anaemia

- The types are
  1. Warm reactive antibody mediated
  2. Cold reactive antibody mediated
  3. Cold hemagglutinin disease
  4. Paroxysmal cold hemoglobinuria
Autoimmune Haemolytic Anaemia

- Warm type antibodies: 70% of cases are Immunoglobulin (Ig) G mediated

- Immunoglobulin G binds at an optimal temperature of 37°C

- Cells coated by the Immunoglobulin G are removed by splenic macrophages that possess Fc receptors

- Immunoglobulin G can fix complement but only up to C3 level
Autoimmune Haemolytic Anaemia

- The resultant C3 coated cell are removed by the cells from the RE but because C3 decays to C3d, which is resistant to engulfment by macrophages

- Part of the red cell is lost during engulfment leading to spherocytes which is characteristic of AIHA

- Therefore the haemolysis of warm antibody AIHA is mostly extra vascular but intravascular may occur
Autoimmune haemolytic anaemia

- Causes of warm antibody autoimmune haemolytic anaemia may be 1° (idiopathic) or 2° (due to autoimmune disease like SLE, Lymphoproliferative disease like B cell lymphomas or chronic lymphocytic leukaemia, infection with Epstein Bar Virus, some ovarian cancers)
Autoimmune Hemolytic Anaemia

• Cold type antibodies: Cold antibodies may occur 1°ly in Cold Hemagglutinin Disease (CHAD) (monoclonal) or secondarily to infections (polyclonal) or neoplasm, autoimmune disorders (monoclonal).

• The immunoglobulin reacts maximally in the cold, and usually is Immunoglobulin M
Autoimmune Haemolytic Anaemia

- The cold thermal amplitude of the antibodies result in the red cells precipitating in the colder parts of the bodies like the hands and feet, nose and ear lobes

- Cold reacting Immunoglobulin M are more likely to give rise to intravascular haemolysis by complement activation but may be extra vascular
Autoimmune Haemolytic Anaemia

- Two infections are most commonly associated with cold type antibodies:

  1. Infection with *Mycoplasma pneumoniae* leads to anti-I Immunoglobulin M cold antiglobulin

  2. Infectious mononucleosis can lead to anti-i Immunoglobulin M cold antiglobulin
Paroxysmal Cold Hemoglobinuria

• It is an intravascular hemolysis that occurs in the cold. It occurs mostly in young adults and children and follows viral illnesses.

• It is caused by the Donath Landsteiner antibody, an Ig G biphasic antibody with anti P specificity

• Diagnosis rests when the serum and red cells are first chilled and then heated to 37°C

• Self limiting and blood transfusion may be given but must keep patient warm
Drug Induced Immune Haemolytic Anaemia

- Mechanism of drug induced haemolysis: Drug adsorption, immune complex mediated, true autoimmune haemolytic anaemia, membrane modification

- Drug that mediated drug induced immune haemolytic anaemia include alpha methyl dopa, sulfa drugs, levodopa, ceftriaxone, procainamide, penicilline, quinidine
Clinical Features Of Immune Haemolytic Anaemia

- Gender is important, both warm and cold AIHA is commoner in females
- A careful drug history is vital in drug induced immune haemolytic anaemia
- Pallor, mild jaundice
- Splenomegaly is usually mild *unless* the AIHA is secondary to lymphoproliferative disease
- Discoloured urine
- Acrocyanosis is a feature of cold type antibodies
Laboratory Investigations

• Full blood count shows anaemia

• Peripheral blood film review will show polychromasia, agglutination, spherocytes and circulating nucleated red blood cells

• Reticulocyte count: increased

• Serum bilirubin: increased

• Urinary urobilinogen: increased

• Definitive diagnosis is by Direct Antiglobulin Test (DAT) and Indirect Antiglobulin Test (IAT)
The arrows show red blood cell agglutination
Polychromatric cells (bluish and slightly larger than surrounding red cells)
Laboratory Investigations

• The DAT is designed to react against Ig G coated or complement coated cells for both AIHA and drug induced immune haemolytic anaemia

• Washed red cells are mixed with the antiglobulin reagent and agglutination observed

• The indirect antiglobulin test detects free antibodies in the patients serum using red blood cells with known antigenic characteristics.

• Alternatively an eluate from the patients red blood cells may be used to determine antigenic specificity
DAT negative positive
Management

• Warm type antibody:
• Corticosteroids
• Intravenous Immunoglobulin
• Splenectomy
• Monoclonal antibody therapy with anti CD20
• Blood transfusion only if heart failure, rapidly dropping hematocrit supervene
• The least incompatible blood is transfused
Management

- Cold type antibodies:
- Alkylating agents e.g Chlorambucil, cyclophosphamide
- Corticosteroids
- Splenectomy
- Plasma exchange
Non immune haemolytic anaemia

- Infections that can cause haemolytic anaemia
  - Malaria
  - Babesia
  - Bartonella
  - Meningococcal sepsis
  - Pneumococcal sepsis
  - Gram negative sepsis
  - Clostridium sepsis
Non Immune Haemolytic Anaemia

- Chemical and physical agents such as drugs, industrial and domestic substances, burns and drowning

- Microangiopathic haemolytic anaemia (MAHA) from Disseminated intravascular haemolysis (DIC), Thrombotic thrombocytopenic purpura (TTP), Haemolytic uremic syndrome (HUS), malignant hypertension

- Mechanical lysis from vasculitis and cardiac prosthesis, cardiac stenosis and patches.
Non Immune Haemolytic Anaemia

- Acquired membrane disorders through liver disease and PNH

- Arsenic, lead, copper, venom from bees, snakes and spiders can cause hemolytic anemia
Pathophysiology of non immune haemolytic anaemia

- Malaria and babesia physically disrupt the red cell membrane of the red blood cell

- Malaria causes haemolysis through direct invasion of the red cells, immune complex formation, splenomegaly and blackwater fever (an intravascular haemolytic anaemia caused by *P falciparum*)

- Bartonella and *Clostrudium Welchii* attack the red cell membranes with enzymes as well as producing haemolysis secondary to Disseminated intravascular haemolysis
Pathophysiology of non immune haemolytic anaemia

- Disseminated intravascular haemolysis is the prototype of microangiopathic haemolytic anaemia

- Disseminated intravascular coagulation (DIC) is a clinicopathologic syndrome in which widespread intravascular coagulation occurs and results in microthrombi formation, fibrin strand deposition, consumption of platelets and coagulation factors.
Pathophysiology of non immune haemolytic anaemia

- Because these pathologies occurs in the microcirculation, they are called microangiopathic hemolytic anaemia (MAHA)

- Thrombotic thrombocytopenic purpura causes haemolysis because of aggregates of platelets in small capillaries with consequent occlusion of the vessels by platelets and fibrin plugs, a form of microangiopathic haemolytic anaemia
Pathophysiology of non immune haemolytic anaemia

• Haemolytic uremic syndrome causes haemolysis because of endothelial damage with fibrin deposition in small vessels, also a form of microangiopathic haemolytic anaemia

• Haemolytic uremic syndrome is characterised by intravascular haemolysis, renal failure and thrombocytopenia

• Other causes of microangiopathic hemolytic anaemia include malignant hypertension
Pathophysiology of non immune haemolytic anaemia

- Acquired membrane disorders: lipids in the red cell membrane are in equilibrium with the plasma. Abnormalities in the lipid of the plasma changes the shape and osmotic fragility of the red cell.

- Vitamin E protects polyunsaturated fatty acids in the red cell against oxidative damage
Pathophysiology of non immune haemolytic anaemia

• Oxidative stress may denature either the globin chain and the heme group leading to the formation of heinz bodies e.g. in Arsenic, lead and copper poisoning, venom from bees, snakes and spiders.

• Chemical and physical agents such as drugs, industrial and domestic substances, burns and drowning can cause hemolysis of the red cell through oxidative hemolysis, membrane damage, osmotic lysis
Pathophysiology of non immune haemolytic anaemia

• March hemoglobinuria causes haemolysis by mechanical lysis
Clinical Features

• A careful history is essential to identify the cause of the haemolysis

• Travel and infection history

• History of blood transfusion

• History of fatigue and jaundice

• Medication and food history

• Vascular or cardiac surgery

• Discoloured urine
Laboratory Investigations

- Full blood count: show anaemia, leucocytosis (infections, monocytosis in malaria), thrombocytopenia in Thrombotic thrombocytopenic purpura, DIC, Haemolytic uremic syndrome)

- Peripheral blood film review may show:
  - Red cell fragments in the peripheral blood film is characteristic of MAHA, DIC, TTP
  - Spherocytes: numerous in burns and drowning
  - Spur cells and acanthocytes in liver disease
  - Oxidative damage shows through heinz bodies
  - Normochromic normocytic
Fragmented red cells and acanthocytes (left)
Laboratory Investigations

• Reticulocyte count: increased
• Serum LDH: increased
• Serum bilirubin: increased
• Serum haptoglobin: reduced
• Urine hemosiderin: it is detected by Perls stain: present
• Hemoglobinuria: present
• Cr Labelled red cell survival: reduced
Management Of Non Immune Haemolytic Anaemia

• Treat the underlying causes