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Hyperhemolysis vs Hypersplenism: A Case Series of Rarities amongst Rarities

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Abstract

Hyperhemolysis syndrome (HHS) and hypersplenism (HS) are two distinct clinical entities that can present with similar manifestations, leading to diagnostic challenges. This article compares and contrasts these conditions, focusing on their pathophysiology, clinical presentation, laboratory findings, and management approaches. HHS, a life-threatening complication of packed red cell transfusion, involves the destruction of both allogenic and autologous red cells, often resulting in a sudden drop in hemoglobin levels post-transfusion. On the other hand, HS is characterized by splenomegaly and excessive sequestration and destruction of blood cells, including red blood cells, white blood cells, and platelets. Differentiating between these conditions is essential for accurate diagnosis and tailored treatment. Management of HHS typically involves intravenous immune globulin and steroids, while HS may require splenectomy or addressing the underlying cause of splenomegaly. Through case reports and clinical scenarios, this article provides insights into the diagnostic and therapeutic strategies for managing these conditions effectively.

Keywords: Hyperhemolysis, Hypersplenism, Rarities

Introduction

Hyperhemolysis (HHS) and Hypersplenism (HS) are two distinct clinical entities with overlapping manifestations, leading to diagnostic challenges. We aim to compare and contrast these conditions, highlighting their key differences in pathophysiology, clinical presentation, laboratory findings, and management approaches. While both conditions can present with sudden fall in haemoglobin levels in patients with hemoglobinopathies, their underlying causes, clinical features, and management strategies differ significantly. Recognizing these distinctions is crucial for accurate diagnosis and tailored treatment.

- **Hyperhemolysis:** Hyperhemolysis syndrome is one of the life threatening complications of packed red cell transfusion characterized by the destruction of both allogenic transfused cells and autologous red cells. One of the main features of hyperhemolysis syndrome is the drop of hemoglobin level lower than that prior to transfusion. It is characterized by the patient's lab values showing evidence of hemolysis (hemoglobinuria, hyperbilirubinemia and raised lactate dehydrogenase), with reticulocytopenia and direct antiglobulin test is often negative [1].
- **Hypersplenism:** Characterized by an enlarged spleen with excessive sequestration and destruction of blood cells, including RBCs, white blood cells (WBCs), and platelets [2]. It can result from any splenomegaly. Hypersplenism is a clinical syndrome characterized by: (i) Splenomegaly (ii) pancytopenia or a reduction in the number of one or more types of blood cells, neutropenia is less common than anemia and thrombocytopenia. (iii) normal production or hyperplasia of the precursor cells in the marrow or a so called maturation arrest (iv) decreased red blood cells survival and (v) decreased platelet survival [4]. This can be:
  - **Primary:** Caused by an underlying splenic pathology, such as Gaucher's disease or primary splenic lymphoma [5].

- **Secondary:** Resulting from other diseases causing splenomegaly, such as portal hypertension or liver cirrhosis, lysosomal storage diseases, thalassemia and sickle cell disease [6].

Pathophysiology

- **Hyperhemolysis:** The possible mechanisms suggested for this syndrome are bystander hemolysis, activation of macrophages and suppression of erythropoiesis. It is important to recognize this condition, as the management of this crisis with additional packed red cells transfusion can worsen the situation of the patient. Latest reports proposed its processes have also been quite similar characteristics to patients with SARS-CoV-2 infections. Like the externalization of phosphatidylserine (PS) on the surface of RBCs, resulting in macrophage erythrophagocytosis while also stimulating complement-mediated intravascular and extravascular hemolysis. Abnormal activation of macrophages is similarly observed in Hemoglobinopathies-associated HHS and SARS-CoV-2 infections [7].
- **Hypersplenism:** Although the exact pathogenesis of hypersplenism-induced peripheral cytopenias is still inconclusive, several mechanisms [8] have been identified:
  a) Retention in the spleen
  b) Enhanced macrophage phagocytosis
  c) Upregulation of cytokines
  d) Gene dysregulation
  e) Autoimmunity.

Clinical Presentation

- **Hyperhemolysis:** Typically presents with symptoms and signs of anemia, including fatigue, weakness, dyspnea, and jaundice. Additionally, depending on the specific cause, patients may experience abdominal pain, fever, or specific organ damage (e.g., kidney failure in hemolytic uremic syndrome). The splenomegaly may or may not be seen depending on underlying condition [9].
- **Hypersplenism:** The symptoms are of 3 types:
  a) Symptoms related to the enlarged spleen such as abdominal fullness associated with feeling of heaviness and discomfort and pain in the left upper quadrant of the abdomen.
  b) **Haematological symptoms:** Symptoms related to thrombocytopenia are common, such as, bruising and epistaxis. Symptoms related to anaemia are fatigue, weakness and pallor. Leucopenia leads to recurrent infections and oral ulcerations.
  c) Symptoms and signs of the underlying diseases.

Laboratory Findings

- **Hyperhemolysis:** Specific laboratory findings depend on the underlying cause. However, common features include:
  - **Anemia:** Microcytic, macrocytic, or normocytic depending on the etiology.
  - **Increased reticulocyte count:** Reflecting increased bone marrow production to compensate for hemolysis.
  - **Elevated bilirubin:** Indicating breakdown products of hemolyzed RBCs.
  - **Specific tests:** Depending on the suspected cause, additional tests like direct Coombs test, G6PD activity, and Diagnostic flowcytometry for PNH or haptoglobin levels might be helpful.
- **Hypersplenism:** Peripheral blood smear might show cytopenias with variable degrees of severity. Other investigations may include:
  - **Laboratory findings:** Anaemia, thrombocytopenia and leucopenia [10].
  - **Evaluation of splenic size:** With physical examination, abdominal Ultrasonography, CT and MRI.
  - **Evaluation of splenic function:** Reduced red cell or platelet survival can be measured by labelling the patient's cells with Cr51 or the platelets with indium and measuring the rate of disappearance of radioactivity from the blood.
  - **Bone marrow aspirate and biopsy:** To rule out primary bone marrow disorders as the cause of cytopenias.

Management

- **Hyperhemolysis:** Most patients improve with intravenous immune globulin and steroids, but in refractory cases, hyperhemolysis may result in multiorgan failure and death in the absence of salvage therapy [11].

There is availability of latest literature where in cases refractory to IVG novel drugs like Eculizumab [12, 13], Tocilizumab [14, 15, 16] & Rituximab [17] were used for post transfusion hyperhemolysis led to rapid clinical responses and no adverse events.

- **Hypersplenism:** Management depends on the primary cause:
  - **Primary hypersplenism:** May necessitate splenectomy or other targeted therapies specific to the underlying disease. Different surgical approaches, including splenectomy, partial splenic embolization, and use of a distal splenorenal shunt, have been used and may result in long-term normalization of the platelet count. Vaccination and prophylactic antibiotics for splenectomized patients.
  - **Secondary hypersplenism:** Treatment focuses on addressing the primary cause of splenomegaly (e.g., treating portal hypertension in cirrhosis).

Excessive bleeding	Hypersplenic thrombocytopenia
Hemolytic syndromes in which splenomegaly further shortens the survival of intrinsically abnormal red blood cells	Hereditary spherocytosis Thalassemia
Mechanical encroachment on other abdominal organs	Calyceal obstruction in left kidney Stomach with early satiety
Severe pancytopenia associated with massive splenomegaly	Hairy cell leukemia Lipid-storage diseases Myeloproliferative neoplasms
Vascular insults involving the spleen	Bleeding esophageal varices associated with excessive splenic venous return due to portal hypertension Recurrent infarctions

Indications for Splenectomy or Radiation Therapy in Hypersplenism.

Case 1: We present the case of a two year old female child with thalassemia major who was referred to our hospital with complaints of hemoglobinuria and poor increment in post transfusion haemoglobin following blood transfusion. The patient had history of recurrent transfusion reactions. The only symptom transfusion reaction was haemoglobinuria during and immediately after the transfusion of packed red cells.

The initial investigations:-
Haemoglobin - 4gm/dl
Hematocrit - 11.6%
Peripheral smear - Suggestive of haemoglobinopathy with sparsely distributed red cells, anisopoikilocytosis, and abnormal cells like tear drop cells, elliptocytes, polychromatophils and spherocytes.
Reticulocyte percentage - 8.16%
Absolute reticulocyte count - 0.135×10^{6} /microliter.

The diagnosis of thalassemia major was reaffirmed through electrophoresis in our Hospital which showed that hemoglobin A 1%, hemoglobin F-96.5% and hemoglobin A_2-2.1%. Considering the past history of transfusion reactions direct antiglobulin test and indirect antiglobulin test were performed and found to be negative. All the other causes of immune mediated hemolysis were ruled out by laboratory work up and clerical/ technical errors have been ruled out by checking the previous records.
Considering the low hemoglobin value of 4gm/dl the patient was planned for 100ml PRBC transfusion. Crossmatching was done with ABO group specific AHG phase compatible unit using gel column agglutination technology. The compatible unit was leukodepleted (post storage leukodepletion) and saline washed thrice (manually under aseptic conditions).Transfusion of the issued unit had to be halted halfway through as the patient experienced haemoglobinuria during the transfusion.
Transfusion reaction workup was done according to the standard operating procedure of the department which ruled out immune mediated hemolysis as both indirect agglutination test and direct agglutination test on the post transfusion sample and direct Agglutination Test using monospecific card also showed negative reaction. The post transfusion lab values exposed hemolysis with LDH-1011 IU/L, Total Bilirubin- 3.2mg/dl and Direct Bilirubin-0.7mg/dl. In the pursuit of cause for hemolysis on transfusion various investigations have been performed. PNH evaluation was performed by flowcytometry which showed no phenotypic evidence of paroxysmal nocturnal hemoglobinuria. Glucose-6-phosphate deficiency was also ruled out as the G-6-PD levels were 26.8 U/ gm of Hb.
Taking into account the repeated transfusion reactions and low hemoglobin again transfusion was planned, this time leukodepleted and saline washed (3 times) packed red cell unit was issued to remove any complement and plasma proteins which might be the cause for the hemolysis. Prior premedication of Inj. Cortisone was given 10 min before the start of the transfusion. However, shortly after the commencement of transfusion the child had haemoglobinuria again due to which the procedure was discontinued. Post transfusion workup was done again in accordance to the departmental standard operating procedure revealing no agglutination either in indirect agglutination test or direct agglutination test. Our patient experienced hemoglobinuria during and after transfusion with DAT negativity, on review of literature similar case report was found. Hence after ruling out all other possibilities and reviewing literature the diagnosis of Hyperhemolysis syndrome was entertained. Considering the diagnosis the patient was put on steroid treatment for a period of 1 week following which packed red cell transfusion was done uneventfully. The post transfusion hemoglobin levels showed increased value of 10.1 gm/dl (Fig 1).

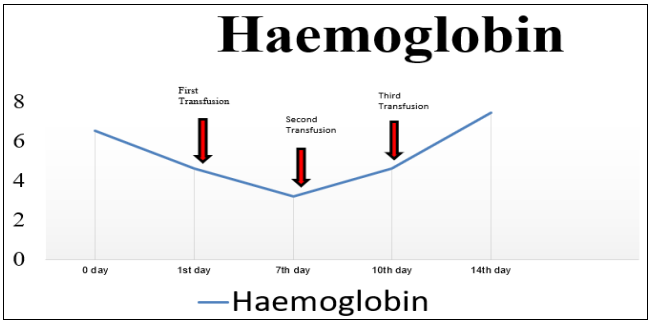

Fig 1: Haemoglobin levels in Case 1

Case 2: A 22-year-old woman who is a known case of E-Beta Thalssemia (NTDT) presented with a two-month history of progressive fatigue and a recent episode of excessive menstrual bleeding lasting seven days. She had no history of fever, chills, night sweats, weight loss, abdominal pain, or easy bruising. Physical examination revealed mild pallor but no other remarkable findings.
Laboratory investigations revealed:

- **Hemoglobin:** 6.5 g/dL (reference range: 12-14 g/dL)
- **White blood cell count:** 3.5 x 10^9/L (reference range: 4-10 x 10^9/L)
- **Platelet count:** 70 x 10^9/L (reference range: 150-450 x 10^9/L)
- **Iron studies:** Normal
- **Vitamin B12 and folate levels:** Normal
- **Liver function tests:** Normal
- **Coagulation studies:** Normal.

A peripheral blood smear revealed no morphological abnormalities in the blood cells. Abdominal ultrasound demonstrated splenomegaly (spleen length: 14.5 cm, reference range: 9-11 cm).
Further investigations, including bone marrow biopsy, viral serologies (hepatitis B, C, and HIV), and autoimmune workup (antinuclear antibody, anti-DNA) were negative, ruling out other potential causes of cytopenia such as bone marrow disorders, viral infections, and autoimmune diseases. Based on the clinical picture, laboratory findings, and negative workup for other etiologies, the patient was diagnosed with hypersplenism.
Management: Given the patient's mild symptoms and the absence of significant life-threatening cytopenias, a conservative approach was initially undertaken. She was monitored with regular blood counts and advised on lifestyle modifications to address fatigue. Due to the menorrhagia, she was started on oral contraceptive pills to regulate her menstrual cycle.
After six months of follow-up, the patient's fatigue improved, and her menstrual cycle became regular with contraceptive therapy. Her blood counts remained stable,

albeit still slightly below normal limits. Given her good clinical response to conservative management, splenectomy was deferred.

Case 3: A 4-year-old boy with a diagnosed case of SCD (HbSS genotype) and a history of recurrent pneumonia presented with a 2-day history of fever, fatigue, and abdominal pain. He denied cough, chest pain, or urinary symptoms. His past medical history included regular blood transfusions and hydroxyurea therapy for SCD management. His last blood transfusion was done 6 days back.

Physical examination:

- **Vital signs:** Temperature 38.8°C (101.8°F), heart rate 140 beats/min, respiratory rate 32 breaths/min, blood pressure 90/60 mmHg.
- Pale skin and conjunctivae, mild abdominal distension, no palpable spleen.

Laboratory investigations:

- **Hemoglobin:** 6.5 g/dL (reference range: 12-14 g/dL) (decreased from pretransfuison level of 9.2 g/dL)
- **Reticulocyte count:** 0.5% (reference range: 0.5-2%)
- **LDH:** 1456 U/L (reference range: 140-270 U/L) (elevated).
- **Direct and indirect bilirubin:** Within normal limits
- **Viral serology:** Parvovirus B19 IgM positive, Parvovirus B19 DNA detected by PCR.

Imaging: Abdominal ultrasound: Splenomegaly (spleen length: 14 cm, reference range: 7.8-9.5 cm for age).

Management: Based on the clinical presentation, laboratory findings, positive Parvovirus B19 testing and splenomegaly on ultrasound, ASSC due to Parvovirus B19 infection was diagnosed. He received aggressive intravenous fluid resuscitation, oxygen therapy, and pain management. Blood transfusions were initiated with packed red blood cells given daily, aiming to raise haemoglobin levels. Additionally, supportive measures like folic acid supplementation were implemented.

Clinical course: Following initiation of treatment, the patient's clinical condition gradually improved. His fever subsided within 2 days, and abdominal pain resolved over a week. Hemoglobin levels progressively increased with transfusions, and serial abdominal ultrasounds showed reduction in spleen size. After 10 days of hospitalization, his clinical picture stabilized, and he was discharged with close follow-up planned.

Case Report 4: A 6-year-old boy with a diagnosed case of beta-thalassemia major since infancy presented with gross hematuria and worsening fatigue two days following a routine blood transfusion. There was no history fever, chills, abdominal pain, or jaundice. His past medical history included regular blood transfusions (28 days interval) and good compliance with iron chelation therapy.

Physical examination

- **Vital signs:** Normal.
- Pale skin and conjunctivae, no icterus, no splenomegaly.

Laboratory investigations: (Table 1)

- **Hemoglobin:** 8.5 g/dL (reference range: 12-16 g/dL) (decreased from pre-transfusion level of 10.2 g/dL)
- **Reticulocyte count:** 1.5% (reference range: 0.5-2%)
- **LDH:** 870 U/L (reference range: 140-270 U/L) (elevated)
- **Direct and indirect bilirubin:** Mildly elevated.
- **Direct antiglobulin test (DAT):** Negative.
- **Paroxysmal nocturnal hemoglobinuria (PNH) test:** Negative by flow cytometry.

Table 1: Lab investigations of the patient day wise

Laboratory Parameters	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 6	Day 6	Day 7
Hemoglobin (12.0–16.0%)	10.2	8.5	7.9	7.8	8.0	8.6	8.9	9.4	9.8
Platelet (150–450 ×10^9/L)	269	257	259	263	249	236	243	221	237
Reticulocyte Count, Absolute (10–150 ×10^9/L)	626.8	373.6	427.6	549.3	321.8	-	-	-	-
Reticulocyte Count (0.2–2.5%)	19.5	13.3	13.8	17.9	10.7	-	-	-	-
Lactate Dehydrogenase (130–230 u/L)	348	2392	1786	988	386	-	-	-	-
ALT (12–49 u/L)	62	113	116	121	-	-	-	67	65
AST (9–49 u/L)	94	133	107	113	-	-	-	86	78

Management: Based on the clinical presentation, laboratory findings, and negative immune-mediated hemolytic workup (DAT and PNH tests), hyperhemolysis was suspected as the primary cause of the presenting symptoms. The patient received supportive care with hydration and pain management. Blood transfusions were temporarily deferred until the hyperhemolysis subsided, and the transfusion service was notified for potential blood component modifications in future transfusions. The patient was started on a synergistic combination therapy of intra-venous methylprednisolone 8mg/kg daily and intravenousimmunoglobulin (IVIg) at a dose of 0.4 g/kg daily for 5-day duration.

Clinical course: Following the completion of steroid therapy, IVIG treatment and supportive measures, the patient's hematuria resolved. LDH levels gradually declined over the next week, indicating decreasing hemolysis. He was then successfully reintroduced to regular blood transfusions with careful monitoring for further complications.

Conclusion

Hyperhemolysis and hypersplenism, despite causing similar cytopenias, arise from distinct pathophysiological mechanisms and require specific diagnostic approaches. Recognizing the differences in their presentation, laboratory findings, and management strategies is crucial for optimal patient care. This article provides a framework for healthcare professionals to differentiate these conditions and guide informed clinical decision-making.

Table 2: Features comparing between Hyperhemolysis and Hypersplenism

Feature	Hyperhemolysis	Hypersplenism
• Splenomegaly	• +/-	• ++ (Definetely)
• Hemoglobin level ↓	• +++	• ++
• Thrombocytopenia	• -	• +
• Leucopenia	• -	• +
• DAT	• -/+	• -
• Bilirubin ↑	• ++	• -/+
• LDH ↑	• +++	• -/+
• H/o of Transfusion	• + (Definetely)	• -/+
• Associated commonly with	• Sickle cell disease, Thalassemia, Myelofibrosis and Lymphoma	• Lysosomal storage disease, Portal Hypertension and Myeloproliferative diseases

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