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Case Report

Iatrogenic Hypersplenism due to Chronic Repeated Blood Transfusion Without Definite Diagnosis

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Received: November 26, 2024; **Published:** December 12, 2024

Abstract

Background: Anemia is a common problem in the neonatal period. Presenting symptoms may suggest numerous possible diagnoses ranging from anemia seen as a normal part of development to anemia due to critical pathology.

Case Presentation: We present the case of newborn girl who was delivered by NSVD full term admitted in NICU on the second day of life by postnatal anemia at the initial examination. She received repeated blood transfusions without approach definite diagnosis this leads to miss-diagnosis and become transfusion dependent that progressed to pancytopenia with reticulocytopenia due to hypersplenism with no signs of hemolysis. This case demonstrates how a poor initial work up leads to miss diagnosis.

Discussion: Early recognition and appropriate interpretation of common symptoms of anemia are challenging for healthcare professionals. Splenomegaly is associated with several abnormalities and anemia which may be lethal if left untreated. Therefore, upon the appearance of the symptoms, it must be treated with a suitable treatment strategy. Splenectomy is an effective treatment option in such cases especially when hypersplenism developed, although further studies are required to evaluate the effects of splenectomy.

Keywords: *Anemia; Hypersplenism; Cytopenia*

Introduction

Anemia is a common blood disorder that occurs when the body has fewer red blood cells than normal. Red blood cells carry oxygen throughout the body using a protein called hemoglobin. If there aren't enough of these cells or this protein, anemia results.

Anemia is often a symptom of a disease rather than a disease itself. In some cases, anemia is temporary and caused by a nutritional deficiency or blood loss. In others, it's the result of a chronic or inherited condition, including genetic disorders, autoimmune problems, cancers, and other diseases. While many types of anemia can be mild and easily corrected, certain types of anemia can be severe, chronic, and/or life-threatening. Severe anemia is commonly treated with red blood cell transfusion. Red blood cell transfusions are used to treat hemorrhage and to improve oxygen delivery to tissues. Transfusion of red blood cells should be based on the patient's clinical condition. Indications for transfusion include symptomatic anemia (causing shortness of breath, dizziness, congestive heart failure, and decreased

exercise tolerance), acute sickle cell crisis, thalassemia, aplastic anemia, and acute blood loss of more than 30 percent of blood volume. So, it is important to take all appropriate samples needed to reach definitive diagnosis before starting blood transfusion.

Discussion

Spleen contain reticular and lymphatic tissue and it is the largest lymph organ. The spleen lies in the left Hypochondriac region of the abdominal cavity between the fundus of the stomach and the diaphragm. It is purplish in color and varies in size in different individual but is usually about 12 cm long, 7 cm wide and 2.5 cm thick. It weighs about 200 grams. [Become palpable when the size is increased to over 14 cm] (Figure 1). The spleen is slightly oval in shape with the hilum on the lower medial border. The anterior surface is covered with peritoneum. It is enclosed in a fibro elastic capsule that dips into the organ forming trabeculae [1]. The cellular material consisting of White pulp which is the main lymphoid tissue of the spleen, it is the accumulation of lymphocytes around an arterial vessel. This aggregation of lymphocytes constitutes the lymphoid tissue known as per arterial lymphoid sheath (PALS) and it is the first to react if microbes reach the spleen through the bloodstream. The central arterial vessels in PALS nodules are branches of the splenic artery. And Red pulp which consists of splenic venous sinuses and cords (of Billroth), (Figure 2) linings of splenic macrophages around the sinuses, form 75% of the spleen and has an essential role in monitoring the integrity of red blood cells [2].

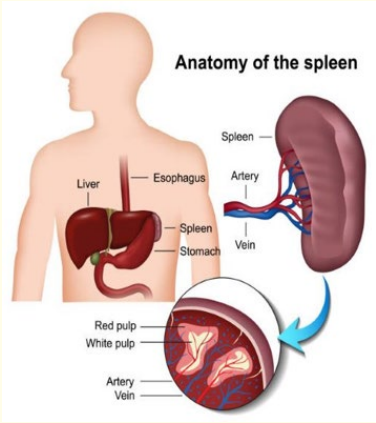

Figure 1: *Anatomy of spleen.*

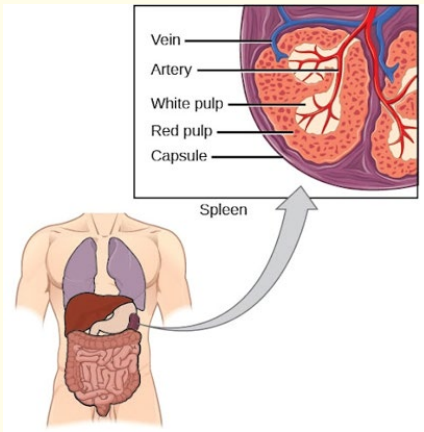

Figure 2: *White and red pulp of spleen.*

The structures entering and leaving the spleen at the hilum 1. Splenic Artery: A branch of the coeliac artery from the aorta 2. Splenic Vein: 3. Lymph vessels "efferent only" 4. Nerves. There are two Blood circulation through the spleen, 10% of blood delivered to it by rapid 1 - 2 minutes through a closed vascular network (Figure 3). 90% of blood delivered to it through an open system (splenic cord) where it is filtered through 1 - 5 µm slits before entering the splenic sinuses, slow 30 - 60 minutes which became more important in Splenomegaly [3].

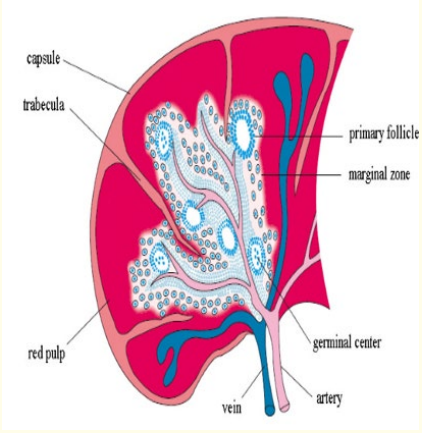

Figure 3: *Internal structure of spleen.*

The primary function of the spleen Filtration of erythrocytes and platelets occurs via splenic cords in the red pulp. Young, flexible red blood cells pass through the epithelial cells of the splenic cords and continue through blood flow. On the other hand, older, larger, and deformed red blood cells are trapped by the splenic cords and phagocytosed by macrophages waiting on the reticulum and sinus endothelium (Figure 4).

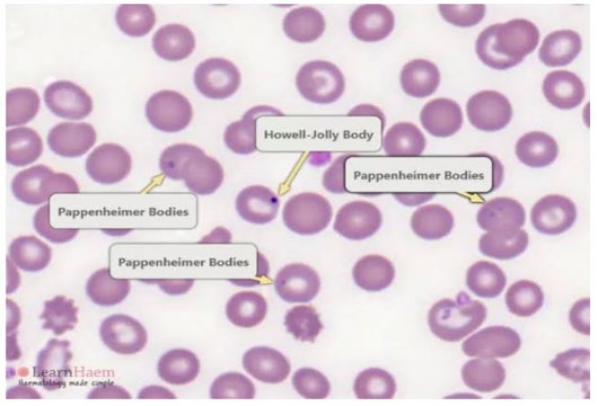

Figure 4: *Howell-jolly bodies and siderotic granules.*

Also, spleen have major role on Transportation of the breakdown products [bilirubin and iron] to the liver via splenic and portal vein. Other cellular material like leukocytes, PLT and microbes is phagocytosed in the spleen. Unlike lymph node, the spleen has no afferent lymphatics entering it, so it is not exposed to diseases spread by lymph. The spleen contains up to 350 ml of blood, and in response to sympathetic stimulation can rapidly return most of this volume to the circulation e.g. in hemorrhage [4].

Infection prevention occurs by two major mechanisms: phagocytic filtration of the bloodstream and production of opsonizing antibodies (Figure 5) macrophages supervise the flow of red blood cells, platelets, as well as microorganisms through the splenic cords [5]. Additionally, in the follicle of the white pulp, infectious antigens and blood-borne pathogens are presented by antigen-presenting cells [6]. This process initiates the activation of T-cells and B-cells, which eventually leads to the production of opsonizing antibodies [7]. After opsonization, macrophages, dendritic cells, and neutrophils phagocytose the antigen [8]. Opsonization is essential to clear particular microorganisms like encapsulated bacteria and intra-erythrocytic parasites (Figure 6).

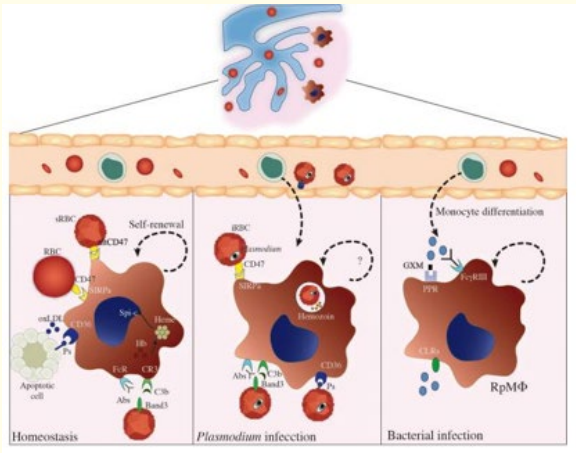

Figure 5: *Pathophysiology of spleen.*

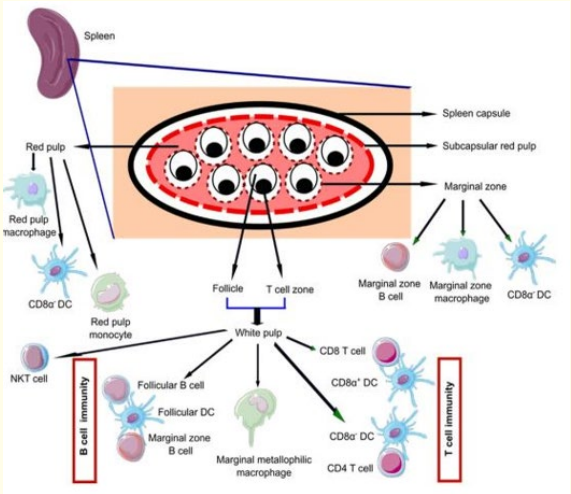

Figure 6: *Spleen in innate and adaptive immunity regulation.*

Hypersplenism is a common disorder characterized by an enlarged spleen which causes rapid and premature destruction of blood cells. It may be associated with an increase in splenic size. The clinical picture of hypersplenism is defined as a peripheral blood cytopenia, which may involve one, two, or three of the circulating blood cells associated with reticulocytopenia. The particular cell line involved has a normal or increased number of precursor cells in the bone marrow. Hypersplenism can be caused by many diseases which, in turn, affects the prognosis of hypersplenism. Thrombocytopenia may exacerbate liver fibrosis [9] and a severe decrease in platelet counts is a major risk factor of hypersplenism [10]. Not surprisingly, the more severe the hypersplenism is, the worse is the prognosis [11]. Splenomegaly and secondary hypersplenism may be associated with acute and chronic infections, autoimmune states, portal hypertension or splenic vein thrombosis, and a number of infiltrative and neoplastic conditions involving the spleen. Our experience and that of others with these various conditions demonstrates that the decision to perform splenectomy should be based on well-defined and often strictly limited indications. Except for idiopathic splenomegaly, the presence and severity of secondary hypersplenism or severely symptomatic splenomegaly should be well documented (Figure 7). The most common physical symptom associated with splenomegaly is vague abdominal discomfort. Patients may complain of pain in the left upper abdomen or referred pain in the left shoulder. Abdominal bloating, distended abdomen, anorexia, and/or early satiety may also occur. More commonly, patients will present with symptoms due to the underlying illness causing splenomegaly [12]. The exam is abnormal if the spleen is palpated more than 2 cm below the costal margin. In massive splenomegaly, the spleen may be palpated deep into the abdomen, crossing the midline of the abdomen, and may even extend into the pelvis [13].

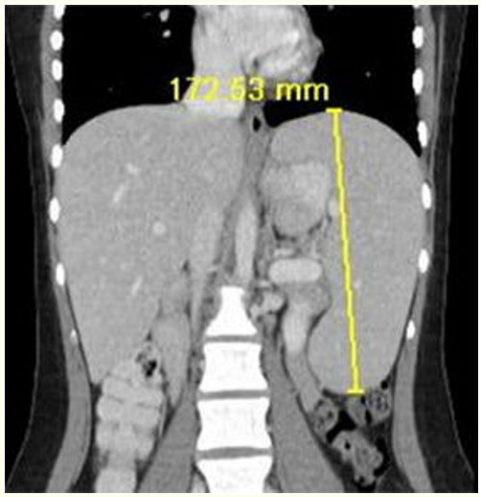

Figure 7: *Splenomegaly-image-in a-12-year-old-girl-with-enlarged-spleen.*

Differential diagnosis includes: Liver disease (cirrhosis, hepatitis) is one of the most common causes, and a history of liver disease, abnormal physical exam findings, and elevated liver enzymes, in addition to abnormal liver imaging, can help diagnose liver diseases [13]. Hematologic malignancies and metastasis shall be especially considered in patients with constitutional symptoms and weight loss. Abnormal peripheral blood smear and biopsy can assist in diagnosing malignancies. Autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) frequently are associated with splenomegaly. In RA, the presence of splenomegaly, in addition to neutropenia, is termed Felty syndrome. Acute and chronic infections, including viral, bacterial, fungal, and mycobacterial infections, can all cause splenomegaly and shall be carefully ruled out. Cytopenias and diseases causing splenic sequestration can be ruled out by complete blood counts, peripheral blood smear, and hemoglobin electrophoresis. Infiltrative disorders such as glycogen storage diseases are rare cause of splenomegaly and shall be considered if other more common causes are ruled out in patients with other clinical

features consistent with these glycogen storage diseases [14,15]. The prognosis for patients with splenomegaly depends on the condition causing the enlargement. Regardless of the underlying etiology, the risk of rupture, even with minor trauma, is high in patients with an enlarged spleen. Splenomegaly is associated with several abnormalities and anemia which may be lethal if left untreated. Therefore, upon the appearance of the symptoms, it must be treated with a suitable treatment strategy (Figure 8).

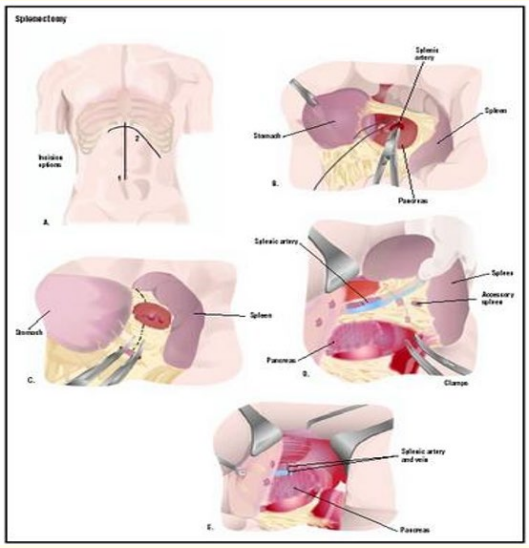

Figure 8: *Splenectomy operation.*

Case Presentation

Our case is a female, Saudi 13 yrs old presented with complications of hypersplenism and huge hepatosplenomegaly due to normocytic anemia since birth managed by repeated blood transfusions without definitive diagnosis that progressed to pancytopenia due to hypersplenism with no signs of hemolysis.

SHE is a full term, normal vaginal delivery, she was admitted to NICU on her second day of life due to postnatal anemia, she stayed for one week at a local hospital she received blood transfusion and phototherapy. She required frequent blood transfusions every 16-20 days. The local hospital also prescribed prednisolone for 1 year with no clear reason and without initial anemia work up. she continued on regular blood transfusion 2 times per month until age of 11 yrs when presented to us with hx of upper quadrant abdominal pain, no hx of vomiting or fever, rashes, joint or bone pain, yellowish discoloration of eyes and urine, night sweats or weight loss. There was no history of similar illness in her family members which included her parents and one sibling, there was +ve consanguinity both parents are healthy.

On physical examination, the patient looks well not distress vitally stable, had pallor but no icterus or lymphadenopathy. Abdomen distended had massive splenomegaly (Figure 9) with firm consistency, regular margin and smooth surface and a non tender, mild hepatomegaly. There was no sign of any neurological deficit and the rest of the systemic examination was normal.

Laboratory studies showed pancytopenia (hemoglobin = 7.5 g/dl, white blood cells = 1.78 x 10^9/L and platelets = 32 x 10^9/L). Examination of peripheral smear showed severe anemia with marked anisopoikilocytosis with microcytic hypochromic blood picture

Figure 9: *11 yrs old female with massive splenomegaly.*

with moderate leukopenia and marked thrombocytopenia. Corrected reticulocyte count was 1.6%. Liver and kidney function tests were normal including serum amylase. Prothrombin time was 14.6 s, APTT was 45.5 s [international normalized ratio (INR) = 1.1]. Serum was ferritin 5779 mcg/l with total iron binding capacity = 420 mcg/dl. Retics 0.35%, Coombs direct and indirect: negative. G6PD: normal, sickling test: negative, electrophoresis HB A: 97% HB A: 2.8% Mantoux test was negative and erythrocyte sedimentation rate was normal. Serological markers for HIV, Hepatitis B and Hepatitis C were negative. Anti DNA, C3, C4: negative, parvovirus B19: not detected, EBV IgM: negative, CMV IgG positive IgM negative. Bone marrow aspiration revealed: hypercellular BM, trilineage hyperplasia, cellularity 80 - 90% megaloblastoid changes, hemopoiesis shoes no evidence of myelodysplasia or involvement by leukemia. All genetic study done was normal.

Ultrasonography confirmed marked diffuse hepatosplenomegaly gall bladder contain numerous small stones, no biliary dilatation, with normal portal vein diameter and no evidence of splenic vein thrombosis. ECHO showed mild Aortic regurgitation.

Our patient managed as multidisciplinary case by recurrent blood and platelet transfusions, vit B12, vitamin D3 drops, iron chelation therapy, ursodiol for dissolving gallstones and folic acid. final recommendation after recurrent admission by same condition with no clear diagnosis was splenectomy and cholecystectomy.

At age of 13 yrs old she received preoperative vaccination As Splenectomy is associated with a lifelong risk of overwhelming infection, she was vaccinated prior to splenectomy: Pneumococcal 23-valent conjugate 0.5 mL IM. *Haemophilus influenza* type b vaccine (Hib - ActHIB) 0.5 mL IM. Meningococcal vaccine (Menactra) 0.5 mL IM. Meningococcal serogroup B (Bexsero) 0.5 mL IM.

Then she underwent successful and effective Splenectomy eliminating splenomegaly related symptoms, improving anemia, thrombocytopenia. The patient reported that she was doing well significantly improved symptoms with no more pallor, gaining weight (Figure 10). At the follow-up appointment, repeat laboratory studies revealed a normal CBC. PLT count rise dramatically in the early postoperative period. Reaching level up to 541.000 mm^3. HB level become 10.2 mg/dL, WBC 15.2 x 10^9/L. The patient no more required any blood transfusion after 2 years follow up.

Figure 10: *13 yrs old female postsplenectomy.*

This case uniquely highlights hypersplenism as complications of repeated blood transfusion. And suggest splenectomy is an effective treatment option in such cases.

Conclusion

Our case finally diagnosed as iatrogenic hypersplenism due to frequent blood transfusion without definitive diagnosis. And also elaborates the importance to make every effort to put the diagnosis in any case of anemia by taking all the appropriate samples before blood transfusion. Splenectomy is the curative treatment of choice in this case.

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Volume 14 Issue 1 January 2025