A Meticulous Review of Diverse Etiologies and Pathophysiology of Anemia in Chronic Liver Disease

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Abstract

Background

Anemia in chronic liver diseases is a common condition with a wide variety of etiologic factors, some of which are life-threatening and need immediate evaluation and intervention. Furthermore, the severity of anemia has been associated with a poor disease prognosis and quality of life of patients. Herein, we have investigated the current literature regarding the spectrum of anemia in advanced liver diseases.

Results

Anemia of chronic disease, gastrointestinal bleeding, malnutrition, iron deficiency anemia and hypersplenism are the common etiologies of anemia accompanied by liver diseases. Medication side effects, viral-induced aplastic anemia and alcohol related hematologic abnormalities constitute the other parts of spectrum of anemia in liver diseases.

Conclusion

Among the various mechanisms of anemia in liver diseases, some are life-threatening and some can be controlled. Investigation of etiology of anemias in chronic liver diseases is recommended, as disease-specific treatments will ameliorate the anemia and enhance patients' quality of life.

Introduction

Anemia is a common multifactorial finding in advanced liver diseases. Malnutrition, gastrointestinal bleeding, hypersplenism, drug side effect and viral aplastic anemia are considered as common etiologies of anemia in cirrhosis patients (1). Paternostro et al, have reported the prevalence of anemia to be 52.9% in cirrhosis patients, with 49.2% of which diagnosed as iron deficiency anemia (IDA). IDA is especially more prevalent in early stages of cirrhosis (2). In other studies the prevalence of anemia among chronic liver disease (CLD) patients have been reported up to two thirds of the patients (3). Anemia in liver cirrhosis is especially noteworthy as it is considered as a marker of disease severity and a prognostic factor. Singh et al, reported a decreasing trend in hemoglobin (Hb) concentration as severity of cirrhosis increases. Thus, anemia has been introduced as a strong predictor of decompensation and poor outcome in end-stage liver disease in various studies (4–6). Anemia also contributes to low quality of life in CLD patients both before and after liver transplantation (7). However a common symptom, the diagnosis of etiologies of anemia in CLD is of utmost importance, as sometimes a life-threatening underlying condition may be present and specific treatments might be applied to alleviate the condition and increase patients' quality of life (8).

Methods

To retrieve the desired information, the current literature were surveyed by searching for anemia, chronic liver diseases, liver cirrhosis and portal hypertension as keywords in Google Scholar, PubMed and Scopus.

A brief review of hemoglobin synthesis and pathophysiology of anemia

A practical classification of anemia, classifies the condition to hypoproliferative anemias, when inadequate hemoglobin is produced and hemolytic anemias, when hemoglobin is prematurely destructed, either in vessels or spleen. Besides, in evaluation of anemia, blood loss should be considered as a potential etiology (9).

A tetramer of polypeptide globin chains, each bound to a heme group consist hemoglobin (Hb). The heme group refers to a central ferrus iron ion (Fe^{2+}) surrounded by 4 porphyrin rings (10). Any condition interfering with synthesis of either heme or globin chains will provoke hypoproliferative anemia. Nutritional deficiency or malabsorption of iron, vitamin B12 and folate, unbalanced hemoglobin synthesis in thalassemia syndromes, disturbed porphyrin synthesis in sideroblastic anemias, bone marrow disorders, renal failure, hypothyroidism, chronic diseases and liver disease constitute the spectrum of the most notable etiologies ultimately resulting in hypoproliferative anemia. Hemolytic anemia is divided into extravascular and intravascular hemolysis. Extravascular hemolysis occurs when the defective RBCs are trapped and destructed in the spleen. The defects might arise from hemoglobinopathies, enzymopathies and membranopathies which are more prevalently hereditary conditions (11). Immune hemolysis, microangipathic hemolytic conditions and infections cause RBCs to be lysed within blood vessels and result in intravascular hemolysis (12).

Portal hypertension

As liver fibrosis progresses in the course of cirrhosis, the vascular resistance of hepatic tissue increases, resulting in portal hypertension (13). Meanwhile, vasodilators including nitric oxide, prostaglandins and vasoactive intestinal peptide are produced to expand the splanchnic blood flow (14). Consequently portal vein dilates and veno-venous shunts form or re-open to maintain the blood flow in portal vein (15). The systemic vasodilatation and arterial under-filling stimulates volume-preserving mechanisms to retain fluid in the circulation. The activation of renin-angiotensin aldosterone and antidiuretic hormone contribute to a hyperdynamic circulatory state (16). When hepatic venous pressure gradient raises above 5 mmHg, gastrointestinal varices appear, the most troublesome of which are esophageal varices with high morbidity and mortality in case of bleeding (17). The pooled blood in spleen alongside with other mechanisms causes splenomegaly as another consequence of portal hypertension (18).

A. Hemodilution

Fluid retention causes hematocrit to be reported lower due to a dilutional mechanism. Such phenomenon happens in hypervolemic states including pregnancy, heart failure, excess fluid administration and of course, cirrhosis (19). Hence, an increase in plasma volume rather than true RBC mass reduction might be

considered in interpreting the laboratory reports in the mentioned conditions. On the other hand, in response to chronic anemia, inhibition of basal endothelium-derived relaxing factor is reduced, leading to vasodilatation and neuro-hormonal compensatory sodium and water retention to increase the cardiac output (20). The anemia-induced hypervolemia, interestingly, exacerbates the hyperdynamic state caused by portal hypertension (21).

B. Splenomegaly

Destructing the old or diseased RBCs is one of the functions of spleen. Hypersplenism refers to the condition of spleen enlargement and one or more peripheral cytopenia in presence of normocellular bone marrow and returning of blood cell numbers to normal after splenectomy (22). The number of any of the blood cells can be affected by hypersplenism, with platelet as the most and RBC as the least sensitive ones (23). To date, various theories have been suggested as pathophysiology of cytopenia in hypersplenism. The most recognized theory associates the increased volume of blood passing the splenic tissue and consequent higher cell destruction (24). According to Shah et al, the phagocytic activity of spleen increases as its size enlarges during the course of cirrhosis leading to excess destruction of RBCs and anemia (25). Due to hypersplenism, in cirrhosis patients the hemoglobin concentration does not increase as effectively as normal population after RBC transfusion (26). Lv et al, reported 91% prevalence of anemia, either alone or in combination with other cytopenias in liver cirrhosis patients with splenomegaly (23). They reported the normalization of blood cell counts in 80.5% of cirrhosis patients after splenectomy in another study (27). Various studies have achieved promising outcomes after splenectomy in cirrhosis patients. Liver fibrosis progression, cytopenias and gastrointestinal bleeding have been ameliorated after the procedure. However, due to risks of operation and infections, splenectomy is not far and wide practiced (28, 29).

C. Gastrointestinal bleeding

Liver cirrhosis patients are a vulnerable group to gastrointestinal (GI) bleeding. Diminished production of coagulation factors in the liver diseases, as well as thrombocytopenia, subject the patients to bleeding tendency, which in addition to portal hypertensive consequences increases the risk of bleeding in the GI tract (30). The most catastrophic GI bleeding occurs in acute esophageal variceal bleeding, which needs urgent management to avoid mortality (31). Bleeding from portal hypertensive gastropathy and gastric vascular ectasia lesions most commonly manifest as chronic anemia in cirrhotic patients. Peptic ulcer is another etiology of chronic bleeding and anemia in this patient population, which forms a smaller proportion of chronic GI bleeding in cirrhosis (32). The most common cause of lower GI bleeding in cirrhosis is hemorrhoids with portal hypertensive colopathy as the second most common etiology. Khalifa et al, reported that 33% of lower GI bleeding in cirrhosis patients needed immediate resuscitation with blood products (33). Portal hypertensive enteropathy can be an obscure source of GI bleeding in cirrhosis (34).

Aplastic anemia

Hepatitis-associated aplastic anemia (HAAA) is a well-recognized and rare phenomenon, defined as pancytopenia and hypocellular marrow occurring two to three months after an acute hepatitis episode. The condition has been reported in all the hepatotropic virus infections including hepatitis A (HAV), B (HBV), C (HCV), D (HDV), E (HEV) and G (HGV) viruses (35). However, in most cases of HAAA no HAV, HBV, HCV association is found. The pancytopenia in HAAA can be extremely severe and sometimes lethal (36). Parvovirus B19 (B19V) and Epstein-Barr virus are other infectious etiologies of aplastic anemia. B19V is previously reported as an etiology of fulminant liver failure and concurrent aplastic anemia (37). The pathophysiology of HAAA is attributed to cytotoxic T cells (CD8+), which recognize hematopoietic and hepatic antigens as similar targets and when sensitized in an acute attack of hepatitis, they destruct the bone marrow cells as well. The process is mediated by gamma interferon (38).

Alcoholic liver disease

Alcohol contributes to anemia in various mechanisms besides the common anemia pathophysiology in general cirrhosis patients. Alcohol has direct toxic effect on bone marrow hematopoietic cells, manifesting as bone marrow suppression and pancytopenia which is reversible after abstinence from alcohol (39). Folate deficiency, either primarily when the patient replaces food with alcohol or secondary to alcohol's effects contributes to megaloblastic anemia. Alcohol decreases the serum level of folate by various mechanisms including increased urinary excretion of folate and decreasing its absorption in jejunum (40). Acetaldehyde, the product of alcohol oxidation in liver, increases the degradation rate of pyridoxal phosphate, the co-factor of aminolevulinic acid synthase enzyme. The enzyme catalyzes a step in heme synthesis. Thus, alcohol causes the defective production of heme and consequent accumulation of unutilized iron in mitochondria forming the so-called sideroblasts (41). Sideroblastic anemia is present in 25-30% of anemic heavy alcohol drinkers and is reversible in cases of alcohol abstinence (42). Sideroblastic anemia occurs in alcoholic patients who have concurrent folate deficiency (43). Another less common mechanism of anemia in alcoholic liver disease is the formation of acanthocytes (spur cells), which can be seen in end-stage liver diseases but is more frequently associated with heavy alcohol consumption (44). Abnormal lipid distribution in RBC membrane deforms the normal cells to acanthocytes. Acanthosis is present in up to 31% of advanced liver cirrhosis patients and is a predicting factor of mortality (45). The spur cells have defective membranes, making them susceptible to hemolysis when passing through spleen (46).

Viral hepatitis

Patients with viral-induced liver cirrhosis develop anemia with mechanisms common with other liver disease including malnutrition, GI bleeding and anemia of chronic disease, as well as unique etiologies attributed to the virus and its treatment (47). As earlier mentioned, rarely viral hepatitis attacks are followed by aplastic anemia in the recovery time, defined as HAAA.

A common therapy regimen for hepatitis C is a combination of pegylated interferon and ribavirin. Ribavirin gets phosphorylated as cells uptake it and to exit the cell for elimination, the drug needs to be de-phosphorylated. As the RBCs lack the essential enzymes for dephosphorylation, the triphosphated

Rivavirin molecules accumulate in the cell, making them susceptible to hemolysis (48). Other authors have suggested that the depletion of ATP during phosphorylation of Ribavirin leads to oxidative stress in RBCs and consequent hemolysis (49). The Interferon-induced hematopoietic stem cell suppression exacerbates the anemia caused by Ribavirin. It is reported that 20% of patients finally need Ribavirin dose reduction to alleviate anemia (50).

Anemia of chronic disease, iron deficiency anemia and iron hemostasis

The ferrous iron (Fe^{2+}) is absorbed by enterocytes of duodenum and jejunum. To enter the blood, the ion is transported via the trans-membrane ferroportin exporter. Ferroportin also exists on membrane of iron-storing cells such as hepatocytes and macrophages (51). Iron is then, mainly transported by transferrin protein in the blood (52). As iron is toxic for the cells, it is stored bound to the ferritin protein in the cells. Hence, blood ferritin levels correlate with amount of iron storage in the body (53). Hepcidin, a peptide hormone produced in the liver, downregulates the release of iron from enterocytes and reticuloendothelial cytes by inhibiting ferroportin. Thus, hepcidin plays a crucial role in iron hemostasis (54).

In chronic inflammatory states like viral infections, organ rejection, inflammatory bowel disease, autoimmune conditions and tumors, an altered cytokine-mediated iron hemostasis results in impaired erythropoiesis. Numerous chronic liver diseases including viral hepatitis and autoimmune liver diseases share an inflammatory background. The pro-inflammatory cytokines including tumor necrosis factor ($\text{TNF-}\alpha$) and interleukin-1, 6 and 10 are the major players to limit the iron availability to the erythrocyte progenitor cells and subsequent erythropoiesis. The changes occur by diminished erythropoietin production, inhibition of duodenal absorption of iron, reduced life span of RBCs, increased macrophage erythrophagocytosis, iron sequestration in macrophages and decreased release of the ion from macrophages (55). Furthermore, hepcidin is an acute phase reactant protein and is highly produced during inflammation, leading to reduced release of iron from enterocytes and macrophages (56). Various previous studies have reported increased expression of pro-inflammatory cytokines and hepcidin in non-alcoholic steatohepatitis (NASH). Obesity-induced inflammation and consequent high hepcidin levels promote to anemia of inflammation in NASH, as the leading cause of chronic liver diseases throughout the globe (57). The anemia of chronic disease (ACD), also known as anemia of inflammation, is initially a mild to moderate normocytic normochromic anemia with decreased reticulocyte count and transferrin saturation level, the two characteristics shared with IDA. ACD and IDA are the leading causes of anemia in chronic liver diseases (3). IDA is a relatively common finding in this patient population which mainly is a result of acute or chronic blood loss from GI tract (58).

Diagnosis of co-existing IDA in chronic inflammation is of great importance, so iron supplementation and further investigation for potential sources of blood loss will be practiced to alleviate the anemia. Serum ferritin level, the indicator of iron storage, can be a useful laboratory parameter to differentiate IDA from ACD. Hepcidin can also be considered to differentiate the two conditions (56). However, diagnoses of ACD in presence of IDA is challenging. Ferritin is an acute phase reactant which despite presence of IDA,

could be raised in inflammation, making it a less reliable test to differentiate ACD and ACD with concurrent IDA (59). Table 1. demonstrates the laboratory parameters in IDA and ACD.

Table 1. The laboratory parameter changes in IDA and ACD.

Anemia etiology	Ferritin	Serum Iron	Transferrin saturation	Hepcidin
IDA	Low	Low	Low	Low
ACD	High	Low	Low	High
IDA+ACD	Variable	Low	Low	Variable

Bilirubin toxicity to erythrocytes

The bilirubin's toxic effect on erythrocytes is a less investigated mechanism in anemia in CLD. Erythrocytes lack the major player of classic programmed cell death (apoptosis), namely nucleus and mitochondria. However, during oxidative stress, hyperosmolarity and several other insults, the erythrocytes undergo a suicidal death, called eryptosis (60). During eryptosis, an influx of Ca^{2+} ions and subsequent activation of Ca^{2+} -sensitive K^{+} channels leads to depletion of cytosolic K^{+} and Cl^{-} ions and cell shrinkage (61). Scrambling of cell membrane exposes phosphatidylserine to macrophages and the diseased RBCs are then recognized by the macrophages and undergo phagocytosis (62). Lang et al, have reported K^{+} efflux, appearing of cell membrane phosphatidylcholine alongside with other manifestations of eryptosis in mice RBCs exposed to bilirubin. Then, they analyzed the number of RBCs undergoing accelerated cell death by detecting phosphatidylcholine as it binds with annexin V. A significant correlation of serum bilirubin levels and annexin V-bound RBCs was reported in the study. Further *in vitro* investigations, revealed increased number of annexin V-bound RBCs when exposed to serum of patients with cirrhosis and hyperbilirubinemia. Albumin was introduced as a protective factor against eryptosis as it binds bilirubin. Low serum albumin was consequently a contributing factor to premature death of RBCs in hyperbilirubinemic states (63). Acidosis is also an exacerbating factor of unconjugated bilirubin toxicity to erythrocytes (64).

Other considerations

In addition to common etiologies of anemia in CLD, exclusive causes might contribute to the condition, depending on the underlying disease. Iron malabsorption in patients with co-existing Crohn's disease exacerbates the ACD (65). Hemolytic anemia is a well-known phenomenon in Wilson's disease (66). Iron overload secondary to chronic hemolytic anemias might end up with liver cirrhosis (67). IDA is associated with celiac disease, a disease linked to increased risk of cirrhosis (68). Various medications cause anemia with different mechanisms. A rare side effect of azathioprine, a medication included in treatment of autoimmune hepatitis, is pure red cell aplasia (69). In a study by Patil et al, antibacterial agents were reported to be associated with a hypocellular bone marrow in cirrhosis patients and cephalosporines were significantly linked to anemia (70).

Conclusion

Anemia is a frequent finding in liver diseases. The condition is a sign of numerous various underlying mechanisms, some of which need investigation and specialized-treatment. IDA, ACD, hypersplenism and GI bleeding are the common etiologies of anemia in CLD. Disease- specific etiologies including viral induced aplastic anemia, malabsorption in inflammatory bowel diseases, hemolysis in Wilson's disease also contribute to exacerbation of the existing anemia. Table 2. summarizes the etiologies of anemia in CLD.

Table 2
Anemia in CLD and their characteristics

Cause of anemia	Pathophysiology/Characteristic
Portal hypertension	Dilutional low hematocrit count GI bleeding Hypersplenism
Viral infections	Cytokine induced aplastic anemia Medication side effect
Alcohol	Malnutrition of B12 and folate Spur cell anemia Sideroblastic anemia Alcohol toxicity to hematopoietic stem cells Alcohol's interactions with folate metabolism
Anemia of Chronic disease	Chronic inflammatory states, cytokine induced
Bilirubin toxicity to RBCs	Eryptosis
Medication side effects e.g. azathioprine, cephalosporines, interferon, ribavirin	Hemolysis Red cell aplasia Bone marrow suppression
Disease-specific	Malabsorption Hemolysis ...

Abbreviations

Anemia of Chronic Disease (ACD), Chronic Liver Disease (CLD), Gastrointestinal (GI), Hemoglobin (Hb), Hepatitis-Associated Aplastic Anemia (HAAA), Non-Alcoholic SteatoHepatitis (NASH), Iron Deficiency Anemia (IDA), Red Blood Cell (RBC)

Declarations

Ethics approval

The study was approved by the ethics committee of the department of Transplantation at Shiraz University of Medical Sciences.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare no conflict of interest.

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No funding was applied for this study.

Authors' contributions

MA searched the current literature and chose the articles to be cited and NA wrote the manuscript. Both authors assisted in preparing the manuscript and reviewed the paper and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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