

Double Deficiency Anemia as a Major Cause of Cytopenias in Patients of Chronic Liver Disease

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ABSTRACT

Background: Chronic Liver disease with cytopenias is common in our set-up. Various causes of cytopenias include double deficiency anemia, iron deficiency, megaloblastic anemia, aplastic anemia and splenic sequestration.

Aim: To determine the frequency of double deficiency anemia as a major cause of cytopenias in adult pts of CLD

Settings and Study design: A cross sectional study was carried out in Pathology Department, KEMU, on 210 patients of CLD from May 2014 to May 2016.

Methodology: Complete blood count was done, peripheral smears made and bone marrow evaluation was done for patients suffering from cytopenias.

Results: Mean age of the patients was 43.4 ± 12.73 years. 164 patients (78.1%) were found to have cytopenias whereas 46(21.9%) patients had no haematological abnormality. In patients suffering from cytopenias, 67(55.8%) patients had combined iron deficiency and megaloblastic anemia. Megaloblastic anemia was found in 8(4.9%) patients. Iron deficiency anemia in 17(10.3%) patients and hypoplastic anemia in 2(1.2%) patients. Hypersplenism was revealed in 126 patients (76.7%).

Conclusion: Double deficiency anemia remains the preventable cause of cytopenias. Prevention of this state will lead to overcoming or delaying the misery and complications related to this disease.

Keywords: double deficiency anemia, chronic liver disease, cytopenia

INTRODUCTION

Chronic liver disease (CLD) results in a progressive destruction of the liver and is a great burden of disease in South East Asia¹. Hematological manifestations of CLD include cytopenias and coagulation abnormalities. Anemia develops in 75%², thrombocytopenia in 64% patients while leucopenia is seen in 5% patients of CLD³.

Causes of cytopenias in CLD include megaloblastic anemia, iron deficiency anemia, double deficiency anemia, aplastic anemia, marrow failure and sequestration of cells in the spleen⁴. In addition, low platelets are also caused by reduced thrombopoietin production by liver⁵ and autoantibodies⁶.

Megaloblastic anemia is caused by the deficiency of folate and vitamin B 12 and thus usually presents with anemia and thrombocytopenia, however, it can present as pancytopenia⁷. This can easily be identified by RBC indices, peripheral smears as well as by the serum levels of vitamin B12 and folic acid.

Iron deficiency contributing to anemia in patients of CLD is mainly due to acute and chronic blood loss that takes place in these patients secondary to portal hypertension⁸. Laboratory diagnosis of iron deficiency anemia relies upon red cell indices on complete blood count as well as detection of tissue iron stores especially through bone marrow aspirate⁹.

The factors implicated to the deficiency of iron, Vitamin B12 and folate include alcoholism, dietary insufficiency and malabsorption of essential nutrients. Combined deficiency of iron, Vitamin B12 and folate in CLD leads to double deficiency anemia which along with other contributing factors lead to cytopenias¹⁰. Hypersplenism is attributed to over activity of spleen leading to sequestration of cells. Hypersplenism is associated with splenomegaly and reduction in at least one cell line in peripheral blood. It

is commonly considered to be another major cause in CLD leading to cytopenias¹¹. Current treatment options, especially for HCV, such as pegylated interferons and ribavirin are also culprit for causing cytopenias in patients¹². When patient develops cytopenias its etiology should be determined and treated accordingly.

The purpose of this study was to determine the frequency of double deficiency anemia as a major cause of cytopenias in adult patients of chronic liver disease. This will help to reduce morbidity in these patients.

METHODOLOGY

A Descriptive, cross sectional study which was carried out in Pathology Department of King Edward Medical University Lahore, from May 2014 to May 2016.. A total 210 patients of both genders between the age 15 – 60 years were included in study. All these patients had chronic liver disease.(Duration of disease for more than 6 months, Evidence of shrunken liver on abdominal ultrasound and signs of portal hypertension, i.e. esophageal varices, ascites, or spider nevi. determined through physical examination). Patients with primary haematological diseases leading to cytopenias i.e. leukemias, lymphomas, and marrow infiltration due to solid tumors and myelofibrosis and patients receiving interferon therapy, radiotherapy or chemotherapy were excluded. Clinical history was taken and relevant physical findings were recorded in the Proforma. 3ml blood was taken in vaccutainer containing EDTA anticoagulant. CBC was done on Sysmex KX 21. Peripheral smears were stained with Wright- Giemsa stain for the manual verification of cytopenias. Bone marrow aspirate and trephine biopsies were done from posterior iliac crest to assess the aetiology of cytopenia.. Bone marrow aspirates were stained with Wright- Giemsa stain and trephine biopsies were stained with Hematoxylin and Eosin. Aspirates and trephine biopsies were evaluated and assessed for cause of cytopenia. Perl's iron staining was performed for the

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evidence of iron deficiency whereas features of megaloblastic picture were evident in Giemsa stain.

RESULTS

A total of 210 patients were included in the study. Patient selected in this study had age ranging from 15 -65 years. Mean age of the patients was 43.4 ± 12.73 years. Out of 210 patients 65 were females (31%) and 145 (69%) were males. 199 patients (94.3%) had CLD due to viral hepatitis while 11 patients (5.7%) had CLD due to non viral causes.

Patients of chronic liver disease were screened for the presence of cytopenias through complete blood counts (CBC) and 164 patients (78.1%) were found to have cytopenias whereas 46(21.9%) patients had no haematological abnormality.

Bone marrow biopsy was performed to determine the cause of cytopenias. 67(55.8%) patients had combined iron deficiency and megaloblastic anemia. Megaloblastic anemia was found in 8(4.9%) patients. Iron deficiency anemia in 17(10.3%) patients and hypoplastic anemia in 02(1.2%) patients. Hypersplenism was revealed in 126 (76.7%) pts

Table 1: Frequency of Peripheral Cytopenias in patients of Chronic liver disease (n=164)

Cytopenia	n	%age
Anemia only	25	11.9
Anemia + Thrombocytopenia	115	54.7
Thrombocytopenia only	06	2.8
Thrombocytopenia+Leucopenia	04	1.9
Pancytopenia	14	6.7

Fig. 1: Bone marrow findings in patients of chronic liver disease with cytopenias.

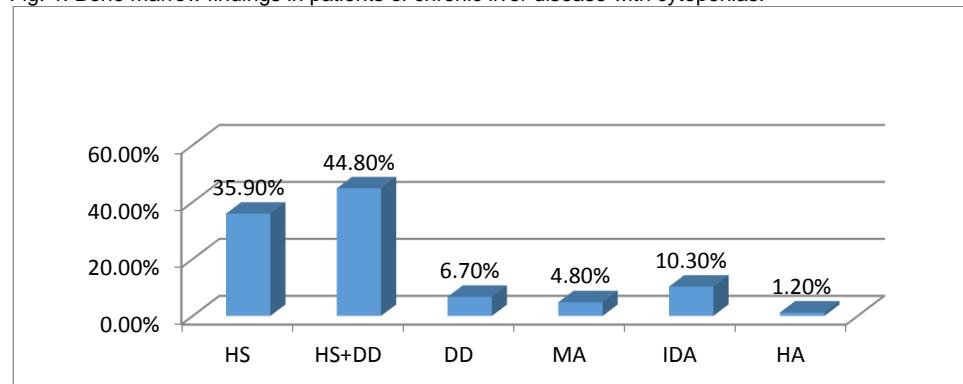


Table 2: Causes of Cytopenias with bone marrow findings

	HS	HS+DD	DD	MA	IDA	HA	ITP	Total
Anemia only			6(2.9%)	2(1.0%)	17(8%)	-	-	25(11.9%)
Anemia+Thrombocytopenia	47(22.3%)	58(27.7%)	5(2.4%)	5(2.4%)	-	-	-	115(54.8%)
Thrombocytopenia only	-	-	-	-	-	-	6(2.8%)	6(2.8%)
Thrombocytopenia+Leucopenia	1(0.5%)	3(1.4%)	-	-	-	-	-	4(1.9%)
Pancytopenia	5(2.4%)	6(2.8%)	-	1(0.5%)	-	2(1%)	-	14(6.7%)

HS: Hypersplenism

IDA: Iron Deficiency Anemia.

DD: Double Deficiency Anemia (Iron Deficiency Anemia and Megaloblastic Anemia) MA: Megaloblastic Anemia.

HA: Hypoplastic Anemia

DISCUSSION

CLD is emerging as a major burden of disease in Pakistan. Khokhar N et al showed 20% of the mortality pertaining to chronic liver disease¹³. The pattern of the liver disease may vary in different geographical locations.

In this study many parameters such as age, sex, viral etiology, cytopenias, splenomegaly and bone marrow examination were studied. The main aim was determination of frequency of double deficiency anemia as a major cause of cytopenias in CLD.

In recent years the prevalence of viral hepatitis is found in much younger ages. In this study the age range was from 15 to 65 years, with a peak in 36-55 years constituting about 60% of our cases. In another study by Shaikh et al, children were not included and results were closer to our results¹⁴.

In our study out of 210 patients 65 were females and 145 were males. 69% of females presented after the age of 35 while about 80% of males presented after this age. The epidemiological pattern of the disease in relation to age and sex distribution reported by Khan et al is consistent with our study¹⁴.

Complete blood count was performed as screening tool for the presence of cytopenias. Among 210 patients, 164 patients (78%) were found to have cytopenia. While 46 patients (22%) had normal complete blood count. Among the causes of cytopenias iron deficiency anemia, megaloblastic anemia, double deficiency anemia and hypersplenism are treatable causes. Timely diagnosis of these conditions can decrease patient's morbidity and mortality to a great extent¹⁵.

It was seen that about two thirds of the patients of CLD developed anemia. In this study 73% patients had anemia. Out of 210 patients, isolated anemia was seen in 25 patients (11.9%), and isolated thrombocytopenia was seen in 06 patients (2.8%). Bicytopenia was also observed as anemia with thrombocytopenia was present in 115 patients (54.8%). Thrombocytopenia and leucopenia was seen in 04 (1.9%) patients. In our study anemia and thrombocytopenia was most common. Qamar et al studied haematological indices in patients with varying degrees of cirrhosis¹³. According to Qamar et al 32% of patients had a combination of thrombocytopenia along with leucopenia. The reason of this fact might be late presentation of the patients in our setup. Due to this late presentation patients

had already developed anemia due to repeated episodes of variceal hemorrhages.

Özatli D and Köksal AS studied type of anemia in chronic liver disease¹¹. Their results showed that iron deficiency anemia was commonest, present in 50% of their patients. In our study anemia was present in 154 (73.3%) patients. Bone marrow examination revealed double deficiency anemia in 11(7.3%) patients, megaloblastic anemia in 08 (5.2%) patients, iron deficiency anemia in 17 patients (11.0%) patients, hypoplastic anemia in 02 (1.2%) patients. Overall in our study, double deficiency and hypersplenism with double deficiency anemia is present in 95 patients (45%) of the cases.

It was observed that 139 (66.1%) of our patients had **thrombocytopenia**. Bashour et al conducted a study to see the prevalence of peripheral blood cytopenias. They concluded that thrombocytopenia was present in 64 % of the cirrhotic patients³ which is in accordance with our results. The cause of thrombocytopenia was evaluated by bone marrow biopsy. Out of 139 patients 05 (3.6%) patient had low platelet count due to **double deficiency anemia**. In 06 cases (4.3%) megaloblastic anemia was causative factor while 120(86.3%) patients had low platelet count due to **hypersplenism**.

Eighteen patients out of 210 cases(8.5%) had **leucopenia**. This is close to the results of the study by Bashour F et al³. Bone marrow morphology in 14 cases (77.8%) was consistent with **hypersplenism**. Shilyansky J also emphasized the importance of thrombocytopenia and leucopenia in hypersplenism and consequent improvement after splenorenal shunt¹⁶. One patient had leucopenia as a result of megaloblastic anemia. One patient had **double deficiency anemia** as cause of leucopenia.

In a study by Kudva MV. 18% of the patients of chronic liver disease presented with pancytopenia¹⁷. In our study out of 210 patients 2% of the patients presented with pancytopenia. The difference may be due to geographical distribution and etiology of liver disease. Ishtiaq et al found hypersplenism along with megaloblastic anemia and aplastic anemia as the commonest cause of pancytopenia in general population¹⁸.

It was observed in our study that out of 120 patients with hypersplenism, 67 patients (55.8%) had associated double deficiency anemia while 53(44.2%) had hypersplenism. One drawback of study is that levels of vitamin B12 and folate were not done in all the patients to determine the etiology of megaloblastic anemia. But in a study by Iqbal SP et al it was shown that vitamin B12 is the commonest cause of megaloblastic anemia in our population¹⁹. Megaloblastic anemia is quite frequently seen in our population²⁰ and in liver disease patients are even more prone to develop vitamin B12 and folate deficiency along with iron deficiency. However, the results of this study clearly show the contribution of double deficiency anemia in patients of CLD to develop cytopenias and thus the clinical complications.

CONCLUSION

Cytopenia(s) are frequent presentation in chronic liver disease. Anemia being the most common, in about 2/3rd of the patient of chronic liver disease. Leading cause of cytopenia(s) in CLD is hypersplenism followed by double deficiency anemia. Double deficiency anemia remains the preventable cause of cytopenias. Prevention of this state

will lead to overcoming or delaying the misery and complications related to this disease.

REFERENCES

- Rafique G, Bukhsh A, Gul A, Khiljee S. Hematologic adverse effects and efficacy monitoring in chronic Hepatitis C patients treated with interferon and ribavirin combination therapy. *Pak J Pharm Sci*. 2017 Jan;30(1):11-16
- Mehta AB, Hoffbrand AV. Haematological aspects of systemic disease., Hoffbrand A, Catovsky D, Tuddenham E.D, editors. Postgraduate Haematology. 5th ed. Massachusetts USA. Blackwell; 2005:973-974.
- Bashour FN, Teran JC. Prevalence of peripheral blood cytopenias (hypersplenism) in patients with nonalcoholic chronic liver disease. *Am J Gastroenterol* 2000; 95: 2936-9.
- Schmidt KG, Rasmussen JW, Bekker C, Madsen PE .Kinetics and in vivo distribution of 111-In-labelled autologous platelets in chronic hepatic disease: Mechanisms of thrombocytopenia. *Scand J Haematol* 1985;34:39-45.
- Lisman T, Leebeek FW. Hemostatic alterations in liver disease: a review on pathophysiology, clinical consequences, and treatment. *Dig Surg*. 2007;24(4):250-8
- GuralnikV, SchafflerA et al. Hypersplenism successfully treated by partial splenic arterial embolisation in a patient with liver cirrhosis. *Dtsch Med Wochenschr* 2008;133:1893-6.
- Elizabeth P. Weinzierl, MD Daniel A. Arber, MD. The Differential Diagnosis and Bone Marrow Evaluation of New-Onset Pancytopenia. *American Journal of Clinical Pathology*, Volume 139, Issue 1, 1 January 2013, Pages 9–29,
- Caldwell SH, Hoffman M, Lisman T, Macik BG, Northup PG, Reddy KR, Tripodi A, Sanyal AJ. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. *Hepatology*. 2006;44:1039–1046
- Gkamprela E1, Deutsch M1, Pectasides D1 Iron deficiency anemia in chronic liver disease: etiopathogenesis, diagnosis and treatment. *Ann Gastroenterol*. 2017;30(4):405-413
- Kumar EH and Radhakrishnan A. Prevalence of Anaemia in Decompensated Chronic Liver Disease. *World J. Med. Sci.*, 10 (1): 56-60, 2014
- Özatli D, Köksal AS et al. Erythrocytes: Anemias in Chronic Liver Diseases. *Hematology*. 2000;5(1):69-76.
- Ong JP, Younossi ZM. Managing the hematologic side effects of antiviral therapy for chronic hepatitis C: anemia, neutropenia, and thrombocytopenia. *Cleve Clin J Med*. 2004;71 Suppl 3:S17–S21
- Khokhar N, Niazi SA Chronic Liver Disease related mortality pattern in northern Pakistan. *J Coll Physicians Surg Pak* Sep 2003;13(9):495-7.
- Shaikh Na, Baloch Aa, Irfan Am et al.Clinical signs of chronic liver disease:is there any difference in patients with hepatitis b and c. *J medical channel* 2010; 16: 233- 36.
- Qamar AA, Grace ND, Groszmann RJ, et al. The incidence, prevalence and clinical significance of abnormal hematological indices in patients with compensated cirrhosis. *Can J Gastroenterol*. 2009; 23: 441–445.
- Shilyansky J, Roberts EA. Distal splenorenal shunts for the treatment of severe thrombocytopenia from portal hypertension in children. *J Gi Surgery* 2007;3: 167-72.
- Kudva MV and Zawai MM. CLD in kuala lumpur, Malaysia: a clinical study. *Singapore Med J* 1990; 31: 368-73.
- Ishtiaq O, Haider Z et al Patterns of pancytopenia patients in a general medical ward and a proposed diagnostic approach. *J Ayub Med Coll Abbottabad* 2004; 16:8-13.
- Iqbal SP, Kakepoto GN et al. Vitamin B12 deficiency- A major causative factor of megaloblastic anemia in patients attending tertiary care hospital. *J ayub med coll abbotabad* 2009; 21:92
- Mannan M, Anwar M, Saleem M et al.Study of serum vitamin B12 and folate levels in patients of megaloblastic anemia in northern Pakistan. *J Pak Med Assoc* 1995, 45:187-18.

