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CHRONIC LIVER DISEASE;
PANCYTOPENIA IN PATIENTS

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ABSTRACT… Objectives: Objective of this study is to evaluate the frequency of pancytopenia in patients with viral chronic liver disease. **Study Design:** Descriptive case series study. **Setting:** All patients enrolled from OPD and admitted patients having a chronic liver disease either due to HBV or HCV at Dow university hospital, Chiniot General Hospital and Zubaida Medical Center Karachi. **Period:** One year starting from January 2016 to December 2016. **Methods:** All patients regardless of age and gender with chronic liver disease due to Hepatitis B or Hepatitis C were included. Patient's age, duration of illness and previous treatments were recorded along with physical examination. Other investigations included complete blood count (CBC) and ultrasound abdomen. Patients with history of alcohol intake, upper gastrointestinal bleeding, or any procedure like sclerotherapy or band ligation, currently taking interferon therapy / history of receiving interferon in the past six months or hepatoma on abdominal ultrasound were excluded. **Results:** Among 224 patients. Male to female ratio was 3.9:1. Mean age was found to be 40.2+3.21. Majority of individuals were between ages 36-45 years. The minimum age was 25 years whereas the maximum age was 65 years. Pancytopenia was found in 28.57 % patients. **Conclusion:** We have concluded that pancytopenia is common in patients with chronic liver disease. Early management can prevent deteriorating outcomes.

Key words: Pancytopenia, Chronic Hepatitis B Infection, Chronic Liver Disease.

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INTRODUCTION

Blood disturbances are common in patients with chronic liver disease. There are various etiological factors for these disturbances. Common etiological factors include acute or chronic gastro-intestinal hemmorrhage. Impaired synthesis of clotting factors by the liver results in deterioration of hemmorhage. Hypersplenism is commonly seen in patients with chronic liver disease. It is due to portal hypertension. Hypersplenism causes secondary hemolysis, It can also cause macrocytosis, megaloblastic anemia, thrombocytopenia and leukopenia. Aplastic anemia can be due to hepatitis or after treatment of hepatitis using pegylated interferon or ribavarins. Interferons cause bone marrow suppression and in this way contributes to anemia. Anemia in setting of chronic liver disease can be complicated further by vitamin deficiencies due to inadequate dietary intake and absorption. The most common cause for chronic liver disease is alcoholism. Alcohol is toxic to bone marrow and thus contributes to pancytopenia. Another explanation is that alcoholics are usually malnourished further contributing to pancytopenia.[1,2] The second most common cause of death in patients with chronic liver disease is acute gastrointestinal hemmorhage due to portal hypertension. It can cause severe hypovolemia and microcytic anemia. Iron deficiency anemia can also develop due to chronic blood loss in the gut due to varices.[3]

Around 76% patients with chronic liver disease demonstrate thrombocytopenia.[4] Thrombocytopenia can vary in severity from mild to moderate to severe. The prevalance of moderate thromocytopenia in cirrhotic patients is reported to be 13% whereas the prevalence of severe thrombocytopenia is 1%. Thrombocytopenia is considered a useful prognostic marker in early stages of the disease.

It is an important predictor of bleeding. There are several underlying mechanisms. Platelet production is decreased due to low levels of thrombopoetin. Hypersplenism causes destruction of platelets further deteriorating the clinical picture. It is hypothesized that there is an intrinsic platelet defect which accounts for impaired function. Platelets should be transfused even if the number is normal due to presence of abnormal platelets. They have reduced adhesiveness and aggregation is impaired.[5] Administration of thrombopoetin can ameliorate the clinical condition but its use is not beneficial due to development of neutralizing antibodies. Administration of cytokines with benefits similar to thrombopoetin might be beneficial. Interlekuin-11 has some role in improving thrombocytopenia however its adverse effects limit its use. Erythropoetin also has some clinical benefits associated with its administration in patients with thrombocytopenia. Some researchers have considered thrombocytopenia as an independent factor for determining prognosis and future occurence of complications.[6]

Hepatitis associated aplastic anemia is a variant of aplastic anemia seen in patients with hepatitis. It is due to loss of hematopoetic stem cells. Viruses such as HBV, HCV, HIV and EBV have the potential to cause aplastic anemia. They can induce lymphocyte activation and ultimaltely apoptosis of stem cells in bone marrow.[7] Hepatitis associated aplastic anemia usually responds to treatment with hematopoetic stem cell transplantation and immunosuppressive therapy.[8-10]

METHODS

This is a Descriptive case series study done over the period of one year starting from January 2016 to December 2016. All patients enrolled from OPD and admitted patients at Dow university hospital, Chiniot General Hospital and Zubaida Medical Center Karachi. All patients regardless of age and gender withchronic liver disease due to Hepatitis B or Hepatitis C were included. Patient's age, duration of illness and previous treatments along with physical examination were recorded. Other investigations included complete blood count (CBC) and ultrasound abdomen. Patients with history of alcohol intake, uppergastrointestinal bleeding, or any procedure like sclerotherapy or band ligation, currently taking interferon therapy / history of receiving interferon in the past six months, hepatoma on abdominal ultrasound were excluded. Data was analyzed using SPSS v.20.

RESULTS

Among 224 patients, 179 were males whereas females were 45. Male to female ratio was 3.9:1. Mean age was found to be 40.2±3.21. Majority of individuals were between ages 36-45 years. The minimum age was 25 years whereas the maximum age was 65 years. Demographic variables are shown in Table-I. Pancytopenia was found in 28.57 % patients. Lab results shown in detail in Table-II.

Variable	No. Patients	Percentage
Gender		
Male	179	79.07%
Female	45	20.92%
Age		
25 to 35 years	59	34.51%
36 to 45 years	112	34.78%
46 to 55 years	39	18.75%
56 to 65 years	14	11.95%
Marital status		
Single	36	21.49%
Married	188	78.53%
Viral marker		
Anti HCV Positive	88	39.28%
HbsAg Positive	98	43.75%
Both positive	38	16.96%
Pancytopenia		
Positive	64	28.57%

Table-I. Demographic variables n=224

Test	Control Values	Means Results
Hemoglobin	< 13.5 g/dl in male	8.21± 1.1
	<11.5 g/dl in female	8.14±0.9
Leukocyte Count	<4 x 10^9 /l	3x10^9±0.5 x 10^9
Platelet Count	< 150 x 10^9 /l	99.5x10^9±8.7x10^9

Table-II. Laboratory results of positive cases n=64

DISCUSSION

Treatment of HBV and HCV using interferons and ribavarin has been associated with development of anemia. 9-13% patients receiving interferon and ribavarin treatment experience significant anemia (i.e hemoglobin < 10g/dL). 30% patients experience moderate anemia (i.e hemoglobin < 11g/dL).[11-13] 25% patients with ribavarin treatment need to undergo adjustments in dose due to severity of anemia. Patients with underlying renal or cardiac problems are at risk of developing anemia in the setting of ribavarin treatment. It has been predicted that fall in hemoglobin level of greater than 1.5 g/dL by 2nd week of treatment is an excellent predictor of future development of severe anemia.[12] Treatment with recombinant erythropoetin has shown good outcome.

Our study shows pancytopenia in 28.57% patients. Majority were males which is similar to Ashraf et al's study. Pur study shows 80% males and 20% females. Ashraf et al's study demonstrates marrow biopsy results of patients with pancytopenia along with hypersplenism secondary to chronic liver disease. Results showed 54% patients with hypercellular marrow, 14% with normocellular marrow, 6.7% with hypocellular marrow and 25.3% with megaloblastic marrow.[14] Oztali et al reports results of his study in which he reviewed files of 500 patients with chronic liver disease. Most common type of anemia was microcytic followed by normocytic and then macrocytic. Most common cause for anemia was iron deficiency anemia which was evident in 50% patients followed by hemolytic anemia due to hypersplenism in 24% patients. Other causes included anemia due to gastro-intestinal blood loss, beta thalassemia, folate deficiency, vitamin B12 deficiency, macrocytic anemia, aplastic anemia and immune hemolytic anemia.[15] Yokus et al reports causes of pancytopenia in 137 cases in Istanbul. The most common cause was vitamin B12 deficiency in 17% cases followed by chronic liver disease in 15% cases. Other causes included malignancy in 13% cases, myelodysplastic syndrome in 13% cases, aplastic anemia in 8% cases, rheumatic diseases in 5% and endocrine disturbances in 2% cases. Authors have concluded that the cause of anemia is dependant on age, sex and co-morbid conditions of patients. Chronic liver disease remains the second most common cause of anemia in these patients. Further it is concluded that vitamin B12 deficiency and chronic liver disease are common in developing countries however malignancy is more prevalent in developed countries of the world.[16] Another study conducted in India reports causes of pancytopenia in 77 patients using bone marrow biopsies. The most common cause was found to be megaloblastic anemia in 68% patients followed by aplastic anemia in 7.7% patients. Myelodysplastic syndromes and hemophagocytic syndrome was found in very few patients.[17] Another study was conducted by Eichner et al in Washington, USA. Eichner et al performed detailed hematologic studies on 65 chronic alcoholics admitted to hospital due to their alcoholism. It was found that 75% patients had hematologic disturbances. Most common cause was folic acid deficiency leading to megaloblasticerythropoesis. 30% had sideroblastic defect in bone marrow. Anemia due to blood loss, hemoorhage, infection and iron deficiency was rarely found. Eichner et al have defined that there are five stages through which a patient with chronic alcoholism leads to anemia. The first stage includes poor nutritional stage which leads to folic acid deficiency without any hematological manifestations. Second stage is known as megaloblastic conversion. This stage begins one week after poor diet following alcohol intake. Third stage is sideroblastic conversion. This stage follows megaloblastic conversion. It can be due to pyridoxine deficiency or intracellular enzyme defect. Next stage is early resolution in which megaloblastic stage disappears. Last stage is the stage of resolution. In this stage hemolysis takes place due to erythroid hyperplasia and reticulocytosis.[18]

Some other hematological manifestations in patients with chronic liver disease include risk of bleeding and thrombosis which can be reduced by the administration of anti-thrombotic medications.[19]

It has been seen that in 6.5% patients, interferon based therapy could not be initiated due to the

presence of thrombocytopenia.[20] Dose reduction is required in 20% patients with ongoing treatment due to thrombocytopenia. Recent studies have concluded that it is safe to administer interferon therapy in patients with platelet count >20,000/ microliter.[21] Various studies have suggested that splenectomy and splenic artery embolization can improve thrombocytopenia however this effect is not permanent.

CONCLUSION

Pancytopenia is common in patients with chronic liver disease. Early management can prevent deteriorating outcomes. Patients with age above 50, should be regularly screened for pancytopenia. Bone marrow examination is rarely required and clinical picture along with baseline investigations is sufficient for construction of diagnosis and initiation of treatment.

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The only way human beings can win a war is to prevent it.

– George C. Marshall –

AUTHORSHIP AND CONTRIBUTION DECLARATION

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