

Bleeding Disorders among a Group of Patients

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ABSTRACT

Objective: To see the frequency and type of various bleeding disorders among patients presenting in haematology outpatients and admitted in medical ward.

Method crosses sectional, Observational study

Result: Bleeding disorder have many underlying causes one investigated. Idiopathic thrombocytopenic purpura, was the more common bleeding disorder seen in our 50 patients followed by bone marrow failure, and coagulation defects and liver disorders.

Conclusion: Bleeding disorder with different etiologies are found in patients presenting with over bleeding in medical wards and critical care units. More work and studies need to be done to explore these underlying disorders

Key words: Idiopathic thrombocytopenic purpura, chronic liver disease, activated partial thromboplastin

INTRODUCTION

Overt bleeding is a common cause of admission in emergency and intensive care units of any hospital. Profuse bleeding is associated with high morbidity and mortality. Among admissions in medical wards various hematological disorders like platelet defects and bone marrow diseases account for a majority hospital admissions followed by cases of acute and chronic liver diseases.¹ In a country like Pakistan the prevalence of hepatitis C is high and this is an important cause of bleeding. Liver is an important site for synthesis for coagulation factors except factor viii, inhibitors of coagulation and proteins involved in fibrinolytic system. Platelets are also affected due to increased consumption and decreased production due to liver insult². This is a cross-sectional, descriptive study, carried out by collaboration between the department of Haematology and Medicine at Fatima Memorial Hospital Lahore, over a period of one year from March 2010 till March 2011.

MATERIALS AND METHODS

All patients who were bleeding and presented in Fatima Memorial Hospital during the study period were included in the study by non probability purposive sampling. Fifty patients were found to fulfill the diagnostic criteria for the study during this time period. A detailed history was taken about fever; weight loss (about 10% in the last six months); bleeding from any site including multiple bruises with minor trauma, purpura, epistaxis, gum bleed, hematemesis, haemoptysis, haematochezia, malena, haematuria, menorrhagia, excessive bleeding from wounds or cuts or after any surgical procedure,

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breathlessness on mild exertion and easy fatigability. General physical examination including pallor; fever; bleeding manifestations in the skin (e.g. bruises and purpura), signs of bleeding from the nose, oral cavity, vagina, anal canal; accessible lymphadenopathy in the cervical, axillary and inguinal region. Hepatomegaly and splenomegaly were sought in abdominal examination and confirmed by abdominal ultrasound.

The cause for bleeding was established in each case by the help of the following investigations. Venous blood samples (2ml) were taken and tested in Sysmex KX 21 for Complete Blood Counts (CBC). Blood films were stained by May-Grunwald-Giemsa stain and peripheral smear was examined for thrombocytopenia, abnormal platelet morphology and for any evidence of bone marrow failure. Another 1.8 ml was tested for prothrombin time (PT), partial thromboplastin time (PTT) and international normalization ratio (INR) was calculated. For prolonged coagulation results correction studies with normal plasma in 1:1 ratio were carried out at 0 hours and after incubation at 37C for 120 minutes to rule out inhibitors. Coagulation factor deficiencies were confirmed by factor assays and Von Willebrand disease (VWD) diagnosis was confirmed by platelet function studies, factor assay for factor VIII and VWF levels.

Bone marrow aspirates were done from right posterior iliac crest where indicated. May-Grunwald-Giemsa staining was performed on the aspirate which was then examined for evidence of dysplasia, erythropoiesis, myelopoiesis and megakaryopoiesis. Myelogram of 500 cells was carried out for blast percentage calculation. The blast cells lineage was confirmed with myeloperoxidase, non specific esterase and Periodic acid Schiff stains. Bone

marrow trephine biopsies were stained by Haematoxylin and Eosin. Cellularity assessment was based on visual examination and graded into three groups; normocellular (30-50% of intertrabecular spaces occupied by haematopoietic cells), hypercellular (>50%), hypocellular (<30%). Cytogenetic testing was carried out in cases of chronic myeloid leukemia, myelodysplastic syndromes and essential thrombocythemia. The data was used to classify patients for bone marrow failures. The patients were grouped in six groups depending upon the disease category given in (Table I). The laboratory characteristics like hemoglobin, total leucocyte count, platelet count for each group are shown in Table II

RESULTS

A total of fifty patients in emergency or critical care unit were identified and their underlying cause of bleeding was established by various tests. The patients were divided into 6 groups as explained in table I column 1 and 2. The specific diagnosis was also categorized as shown in Table I, column³, The maximum number of patients were seen in the platelet disorder group¹⁷, which included idiopathic thrombocytopenic purpura¹², Evans syndrome¹, Gestational thrombocytopeni¹, Bernard soulier syndrome² and essential thrombocythaemia¹. The second most frequent category for bleeding came in the bone marrow failure group¹⁴ among which aplastic anaemia was found the most frequent⁵ followed by myelodysplastic syndrome⁴ and leukemia³. Chronic liver disease with cirrhosis was the underlying pathology in 7 case, however acute liver failure were only two cases. Amongst coagulation factor deficiency the most frequent factor deficiency was von Willebrand disease⁴, followed by hemophilia³ and factor xiii deficiency¹. Itrogenic group included drugs like anticoagulants and platelet antagonists accounted for 5 cases of severe bleeding episodes.

Gender distribution showed there were 18 males and 32 females. Males presented in the first 2 decades of life with bone marrow failure in the 2nd – 4th decade with platelet disease or defect. Females presented in the 2nd and 3rd decades with bone marrow failure, in all ages with drug overdose, factor

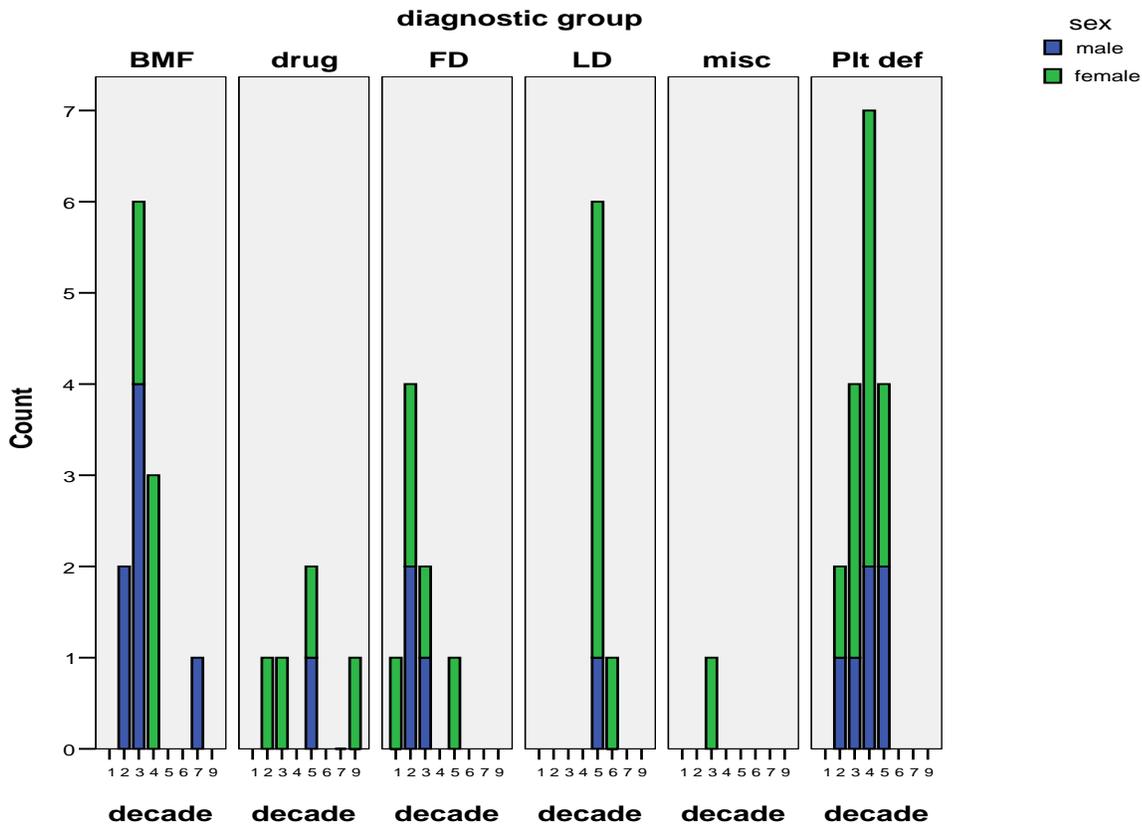
deficiency and platelet defects. When the two tailed significance of paired t test was calculated for age of presentation and sex , p value was less than 0.001. The mean age of acquired causes of bone marrow failure and ITP was around 30 years while the hereditary causes of coagulation factor deficiency presented in the second decade. As the main underlying disease was vWD the most common presentation was menorrhagia in two of the cases and intraperitoneal bleed from luteal cyst in 2 cases. Those with factor xiii deficiency presented with intracranial bleed and hemophilia presented after roadside trauma in 2 cases and following tooth extraction in one case.

The most frequent diagnosis was ITP. The mean age of ITP was 30.55 years. Haemoglobin was 9.49+/- 2.8; TLC was 6.93x 10⁹/l; Platelet count was 13454.5 +/- 9092.5. The most common presentation of bleeding was severe menorrhagia in females and upper GI bleed presenting as malena in males. Cirrhosis was the underlying disease resulting in haemorrhage from gastrointestinal tract in 5 cases and 2 cases presented with fulminant hepatic failure and marked coagulopathy.

Table I (n=50)

Diagnostic group	=n	Final diagnosis	=n
Platelet disorders	17	ITP	12
		Evans syndrome	1
		Gestational thrombocytopenia	1
		Bernard Soulier Syndrome	2
		Essential thrombocythemia	1
Bone marrow failures	12	Aplastic anaemia	5
		MDS	4
		Leukemia	3
Coagulation factor deficiency	8	vWD	4
		Hemophilia	3
		fact 13 deficiency	1
Liver disease	7	Cirrhosis	5
		Fulminant hepatic failure	2
Drug side effect	5	Anticoagulant	3
		Platelet antagonists	2
Miscellaneous	1	Polycystic ovary	1

Diagnosis group	=n	age	Haemoglobin g/dl	TLC x 10 ⁹ /l	Platelet count x 10 ⁹ /l
Platelet disorders	17	32.2+/-10.2	9.8+/-2.7	7.6+/-3.1	70190+/-21394
Bone marrow failure	12	29.9+/-12.9	5.5+/-1.99	5.4+/-0.6	66500+/-180
Factor deficiency	8	19.6+/-9.8	8.2+/-2.9	5.5+/-0.9	262125+/-90308
Chronic liver disease	7	50.7+/-4.49	9.1+/-1.4	8.9+/-4.2	105142+/-30333
Drugs	5	44.6+/-2.3	6.5+/-3.2	11.3+/-2.7	353800+/-15193
Miscellaneous	1	25+/-0	10.9+/-0	6.7+/-0	350000+/-0
Total	50	33.4+/-15	8.15+/-2.9	7.3+/-4.2	138864+/-19140



DISCUSSION

Recent evidence has come to light suggesting a shift from our prior understanding of pathophysiology of immune thrombocytopenia. It was firmly believed that thrombocytopenia resulted from antibody-mediated platelet destruction only. The new information developed is that the same antibodies that mediate platelet destruction also mediate impaired platelet production by damaging megakaryocytes and/or blocking their ability to release proplatelets³. An exciting but to-be-explored area involves the role of platelet reactive cytotoxic CD8+ cells. These cells clearly exist, but their clinical relevance is not known. Finally, an area of intensive investigation involves T-regulatory cells, which have been reported to be deficient in ITP in several studies. In our study ITP was seen in predominantly in females with a mean age of 30 years. Another study carried out in Lahore reports similarly with peak incidence in the 3rd decade and female to male ratio 3:1. They concluded that adult ITP is predominantly seen in young females, presents with bleeding from more than two sites⁴. We found similar clinical presentation with bleeding from more than one site.

Coagulation factor deficiencies were seen in 8 patients. vWD was the most common followed by haemophilia A. In a study carried out at Rawalpindi haemophilia was found in 62% bleeding patients while vWD was only found in 18% patients. VWD is considered an underdiagnosed entity in our population⁵. Bone marrow failures resulting in severe symptomatic thrombocytopenia were seen in 12 cases. The mean platelet count for this cohort was 16000/mm³. The mean Hb was 5.5 g/dl for this group. Platelet count of less than 10000/microlitre is associated with spontaneous bleeding. Coagulation abnormalities and thrombocytopenia are commonly seen in patients who are suffering from chronic liver disease or are anti HCV carriers. Such patients have a greater incidence of bleeding events. Severe coagulopathy is seen in both acute and chronic liver disease. This accounts for increased morbidity and mortality among these patients. Chronic liver disease is responsible for various hematological and coagulation disturbances through a varied mechanism⁶. Thrombocytopenia due to increased splenic sequestration and low thrombopoietin levels is frequently seen in chronic liver disease patients. Both leucopenia and leucocytosis is seen alongwith

reduced red blood cell survival leading to hemolytic anemia. In our study a total of seven chronic liver disease sufferers were included who were already diagnosed for their primary illness. Five patients were with chronic liver disease and two of them were of acute liver failure. All had thrombocytopenia.

Their presetting symptoms included hematemesis, melena, purpura and hepatic encephalopathy. The estimated prevalence of hepatitis C is reported to be 5-8 %. The association of hepatitis C and thrombocytopenia (cut off value <150,000/ul) has been studied at the department of King Edward Medical University. It was seen in this study that bone marrow had increased number of megakaryocytes. A similar study was done in the pediatric department of Khyber teaching hospital Peshawar Pakistan in which 50 children presenting with bleeding through any orifice were included and a reduced platelet count was found in 38 children⁸.

Coagulation abnormalities and thrombocytopenia are commonly seen in patients who are suffering from chronic liver disease and are antiHCVcarriers. Such patients have a greater incidence of bleeding events⁹. Severe coagulopathy is seen in both acute and chronic liver disease. This accounts for increased morbidity and mortality among these patients¹⁰. Chronic liver disease is responsible for various hematological and coagulation disturbances through a varied mechanism. Thrombocytopenia due to increased splenic sequestration and low thrombopoietin levels is frequently seen in chronic liver disease patients. Both leucopenia and leucocytosis is seen alongwith reduced red blood cell survival leading to hemolytic anemia⁵. In present study a total of seven liver disease sufferers were included who were already diagnosed for their primary illness. Five patients were with chronic liver disease and two of them were of acute liver failure. All had thrombocytopenia. Isolated factor x deficiency has also been studied in Northern Pakistan where rate of consanguineous marriages is high. As it is an autosomal recessive disorder rare in American and European populations and was found to be present in 24 patients out of a total of 571 patients presenting with bleeding¹¹.

Therefore looking at the studies done retrospectively it is seen that bleeding disorders are common once investigated for any patient who presents with bleeding from any site of body. Preexisting co-morbidities in any patient also contribute towards the final diagnosis of bleeding diathesis.

CONCLUSION

Platelet defects were the most common disorders in our selected population of bleeding patients and idiopathic thrombocytopenic purpura was on the top followed by other platelet defects. Twelve cases of bone marrow failure were the next common etiology for bleeding. Coagulation defects in the form of von willibrand disease, hemophilia and factor viii deficiency were also diagnosed in our patients. Coagulopathy was seen in patients with liver pathology both acute and chronic.

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