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STUDY OF EVALUATION OF VARIOUS CAUSES OF THROMBOCYPTOPENIA IN PATIENTS ADMITTED AT OUR HOSPITAL

Pathology

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ABSTRACT

Background: Thrombocytopenia is one of the commonest cause of bleeding. Thrombocytopenia can result from decreased production from the bone marrow, increased platelet destruction, abnormal sequestration and pooling. Though thrombocytopenia is not purely a disease, but it is an important clinical and diagnostic manifestation seen in many diseases. Clinical presentation of thrombocytopenia varies, from being devoid of symptoms to presenting with bleeding episodes. Though, it does not have an absolute relationship, degree of thrombocytopenia correlates with degree of bleeding manifestations.

Objectives: The main objective of this study is to do a detailed clinicopathological correlation of various cases of thrombocytopenia in adults presenting to a tertiary care hospital. This study aimed to find the age and gender distribution of the cases, various etiological factors, severity of thrombocytopenia and relationship of platelet count with bleeding manifestations.

Materials and Methods: This is a two-year cross sectional study carried out in the Pathology Department of Ispat General Hospital, Rourkela, Odisha from May 2012 to April 2014. All the samples of indoor patients coming from different departments of our hospital for Complete Blood Count & Peripheral smear examination were screened and the cases having platelet count of < 1.5 lakhs/mm3 were included in our study.

Results: In this study, we found that the incidence of thrombocytopenia was 2.8% (253/9000) during the period of two years. The commonest cause found to be Infections followed by anemia and other causes. Among the infections, malaria accounted for maximum cases followed by septicemia. Among the cases of anemia, combined deficiency anemia accounted for maximum number of cases followed by megaloblastic anemia. Our study also found a strong association between the decrease in platelet count and the percentage of cases with bleeding manifestation.

KEYWORDS

thrombocytopenia, bone marrow, platelet count, bleeding, blood count, peripheral smear

INTRODUCTION

Thrombocytopenia is defined as platelet count less than 1.5 x10^5/µl. Thrombocytopenia is one of the commonest cause of bleeding [1,2]. Thrombocytopenia can result from decreased production from the bone marrow, increased platelet destruction, abnormal sequestration and pooling [3]. Though thrombocytopenia is not purely a disease, but it is an important clinical and diagnostic manifestation seen in many diseases. To know the etiology of thrombocytopenia we need to run a battery of investigations from a simple routine investigation like complete blood count to bone marrow examination. Sometimes thrombocytopenia is a true scratch in the head for the clinician. The management of thrombocytopenia is dependent on the etiology, and the degree of severity with which it presents [4]. Clinical presentation of thrombocytopenia varies, from being devoid of symptoms to presenting with bleeding episodes. Though, it doesn't have an absolute relationship, degree of thrombocytopenia correlates with degree of bleeding manifestations [5]. Available comprehensive studies on thrombocytopenia are few. Hence this study attempted to find the various etiologies of thrombocytopenia in hospitalized patients.

OBJECTIVES: The main objective of this study is to do a detailed clinicopathological correlation of various cases of thrombocytopenia in adults presenting to a tertiary care hospital. This study aimed to find the age and gender distribution of the cases, various etiological factors, severity of thrombocytopenia and relationship of platelet count with bleeding manifestations.

MATERIAL AND METHODS

This is a two-year cross sectional study carried out in the Pathology Department of Ispat General Hospital, Rourkela, Odisha from May 2012 to April 2014. All the samples of indoor patients coming from different departments of our hospital for Complete Blood Count & Peripheral smear examination were screened and the cases having platelet **count** of < 1.5 lakhs/mm^3 were included in our study.

Inclusion Criteria

The cases who had platelet count of <1.50 lakh /mm^3 irrespective of the age group were included in the study.

Exclusion Criteria

Out patients were not included in the study as detailed case sheets were not available to retrieve data.

Materials & Methods

Hb, total count, differential count and platelet count were done on 5-part automated blood cell counter (Beckman Coulter) and platelet count was counterchecked on peripheral blood smear.

Peripheral smears made from venous blood collected in EDTA tube after being stained by Leishman stain, were examined under high power & oil immersion for RBC morphology, Differential WBC count, parasite if any & platelet count by manual platelet was done by counting ten consecutive fields in the representative area, taking the mean & multiplying it by 10,000 or 15,000 depending upon the width of the eye piece and the count was given in per mm^3. The EDTA tube was checked for presence of any blood clot. The smears were studied for presence of platelet aggregates and platelet satellitism to rule out pseudothrombocytopenia. If it was present, the samples of the respective patients were repeated using citrate bulb and were screened again and if found normal they were excluded from the study. Investigations like reticulocyte count, ESR & bone marrow aspiration were done wherever necessary. Complete medical history and examination were retrieved from the case files. Hematology & other laboratory test results were correlated with clinical findings to decide the etiology of thrombocytopenia and relation of degree of thrombocytopenia with severity of clinical manifestations and with etiology. Statistical analysis to show association between platelet count and bleeding was done by calculating chi-square test by using MedCalc software Version 13.2.2.

OBSERVATIONS AND RESULTS

Total number of cases of thrombocytopenia which formed the study group during the period of two years from May 2012 to April 2014 were 253. This comprised 2.8% i.e.253 (Table No 1) out of 9000 of the total requisitions received from the indoor patients of our hospital in the hematology section of the Department of Pathology.

Table No.1: Percentage of cases of Thrombocytopenia

Total No of requisitions from indoor departments	Cases with Thrombocytopenia	Percentage
9000	253	2.8%

Table No.2: Agewise and Gender wise distribution of Cases Presenting with Thrombocytopenia

S. NO	Age group in years	Male (M)	Female (F)	Total No.	Percentage
1	<1 year	21	10	31	12.25
2	1-10	7	2	9	3.55
3	11-20	15	9	31	12.25
4	21-30	31	15	46	18.18
5	31-40	25	13	38	15.01
6	41-50	25	12	37	14.62
7	51-60	22	9	31	12.25
8	61-70	18	05	23	9.09
9	71-80	10	1	11	4.34
10	81-90	2	-	2	0.79
11	91-100	1	-	1	0.39
	TOTAL	177(69.96%)	76 (30.04%)	253	100

The age of patients in our study was ranging from 1 day to 91 years: The commonest age group for thrombocytopenia was between 21-30 followed by 31-40 & 41-50 accounting for 46(18.18%), 38(15.01%) and 37(14.62%) cases respectively. Out of 253 cases 177 (69.96%) were males and 76 (30.04%) were females. A definite male preponderance was seen in overall picture as well as in almost all age groups. The overall male to female ratio was 2.32:1.

Table no.3: Shows Distribution of cases according to etiology of Thrombocytopenia.

Sl/No		No. of cases	Percentage
1	Isolated etiology	227	89.72
2	Multiple etiology	21	8.30
3	Unexplained etiology	5	1.98
	Total No.	253	100

There were total 253 cases, 227 (89.72%) of which had isolated etiology, 21 (8.30%) of which had more than one etiology & 5 (1.98%) of which had unexplained etiology.

Table no.4: Shows Various isolated causes leading to Thrombocytopenia.

S No.	Causes	Percentage
1	Infection	99 (39.13%)
2	Anemia	67 (26.48%)
3	Use of myelosuppressants	10 (3.95%)
4	Alcoholism	10 (3.95%)
5	Obstretic causes (P.I.H, Abruptio)	9 (3.56%)
6	Snake bite	8 (3.16%)
7	Haematological malignancies	7 (2.77%)
8	Traumatic brain injury	2 (0.79%)
9	Moderate splenomegaly	1 (0.39%)
10	ITP	1 (0.39%)
11	DIC	1 (0.39%)
12	Miscellaneous	12 (4.74%)
	TOTAL	227/253 (89.7%)

Infection was the leading cause of thrombocytopenia in 99/253 (39.13%) cases followed by anemia in 67/253 (26.48%).

Table no.5: Shows the Distribution of cases of infection leading to thrombocytopenia.

Causes	No. of cases	Percentage
Malaria	40/253	15.81%
Septicaemia	21/253	8.30%
Viral fever (other)	21/253	8.30%
Bacterial infection	7/253	2.77%
Tuberculosis	2/253	0.79%
Dengue	6/253	2.37%
Viral hepatitis	1/253	0.39%
HIV	1/253	0.39%
TOTAL	99/253	39.13%

Malaria formed the leading cause of infection causing thrombocytopenia in 40/253 (15.81%) cases, Septicaemia and viral fever were the next common causes of infection causing thrombocytopenia present in 21/253 (8.30%) cases each.

Table no. 6: Distribution of cases of anemia leading to thrombocytopenia.

Type of anemia	No. of cases	Percentage
Combined deficiency anemia	45	17.78%
Megaloblastic anemia	17	6.72%
Aplastic / hypoplastic anemia	2	0.79%
Anemia of chronic disease	2	0.79%
Iron deficiency anemia	1	0.40%
TOTAL	67/253	26.48%

The total number of cases of anaemia leading to thrombocytopenia were 67/253(26.48%). The maximum number of cases were of combined deficiency anaemia i.e. 45/253 (17.78%) cases. Megaloblastic anaemia was the next most important cause of anaemia leading to thrombocytopenia in 17/253 (6.72%) cases. Aplastic or hypoplastic anaemia is the cause in 2/253 (0.79%) cases, Anaemia of chronic diseases, and Iron deficiency anaemia lead to thrombocytopenia in 2/253 (0.79%) & 1/253 (0.40%) cases.

Table no. 7: Relationship of platelet count and bleeding manifestation

Group	Platelet count/cmm	Total no. of cases	Causes of bleeding	% of patients with bleeding
I.	1 to 1.5 L	77	5	6.49%
II.	0.5 to 1 L	98	4	4.08%
III.	0.2 to 0.5 L	55	6	10.91%
IV.	<0.2 L	23	5	21.73%
	TOTAL	253	20	7.90%

The total number of cases which presented with bleeding was 20/253 (7.90%). The maximum number of cases of thrombocytopenia which had bleeding had platelet count of <20,000 and were 5/23 i.e. (21.73%). The chart indicates the risk of bleeding increases as platelet count decreases. Bleeding manifestation was present in 79 /1012 (7.8%) cases. The major site of bleeding was in the form of petechiae and purpura, followed by gastro intestinal bleeding.

DISCUSSION

Out of the 9000 patients admitted 253 were selected as per the inclusion criteria in this study. The incidence of thrombocytopenia in our hospital is found to be 2.8%. In this study, we found Infection as the leading cause contributing to thrombocytopenia accounting for 39.13% of the total cases of thrombocytopenia, which is in accordance with the study conducted by Alam et al study [6] and it comprised 70.7% of the total cases. Though the leading cause was same there was a variation in the percentage and this can be attributed to geographical variation. Among the cases of infection malaria was the leading cause of infection, causing thrombocytopenia accounting for 15.81%, this finding was similar to the study conducted by Alam et al [6] and it was present in 43.2% cases. The difference in percentage can be attributed to the difference in prevalence of malaria in different geographical areas. Malaria causes thrombocytopenia by increased immune mediated platelet destruction. It is not an unexpected finding to find malaria as a leading cause of infection, malaria being endemic to this area.

Thrombocytopenia is a frequent complication of malaria frequency of which given by different studies is highly variable. Sitalakshmi et al had reported thrombocytopenia in 15 to 96.97% malarial cases [7]. Malaria in our study was encountered in all age groups and the platelet count ranged from 15,000/µl to $1.35x10^5$/µl. Thrombocytopenia accompanying malaria is characteristic and it can be used as an indicator of malaria in patients presenting with pyrexia of unknown origin.

Both thrombocytopenia and platelet-induced clumping are associated with severe malaria and especially with Cerebral Malaria. Thrombocytopenia results from widespread clumping in sequestration sites, the degree of which is directly linked to the patient's parasite burden and it was found in a study by Samuel et al [8].

The second most important cause of infection causing thrombocytopenia was septicemia. Sepsis causes thrombocytopenia by immune mediated platelet destruction. In all cases of septicemia in infant's microbiological studies were done and blood culture revealed staphylococcal as the most common causative organism followed by enterobacter. Torkaram et al, Guida et al found that sepsis is a common cause of neonatal thrombocytopenia and is mainly due to the presence

of Enterobacter and gram negative organism [9, 10]. Charo B and Iqbal J concluded late onset thrombocytopenia as an important risk factor in NICU [11]. Murray NA in his study stated that 8% of preterm and 6% of all neonates admitted to an NICU have severe thrombocytopenia [12]. Preterm neonate from a mother with pre -eclampsia who develops early bacterial sepsis and a baby with intrauterine growth restriction who develops necrotizing enterocolitis may both become thrombocytopenic because of underlying impaired platelet production (after pre-eclampsia or intrauterine growth restriction) combined with platelet consumption (during sepsis or NEC) [12]. Septicemia was found to be common in the neonates in our hospital, this would be explained by the fact that ours is a referral hospital and number of patients who present are in late stages of disease.

Viral fever was found to be responsible for thrombocytopenia in 8.30% cases. Thrombocytopenia associated with viral infection is as a result of decrease in the production of platelets from megakaryocytes.

The other causes of thrombocytopenia in infections were bacterial infections present in 2.77% cases. Infection was found to be present in all age groups; however, septicemia was predominantly seen in neonates. The platelet count ranged from 15,000/cmm to 135000/cmm with the maximum cases having moderate thrombocytopenia with platelet count in between 50,000/cmm to 1 Lakh/cmm. It is unfortunate that preventable condition like infections cause thrombocytopenia leading to a lethal outcome. Infection is a preventable cause, of thrombocytopenia, hence by use of proper serological, microbiological tests and taking the support of leukocytosis on peripheral smear, with raised ESR, C reactive protein early diagnosis can be made and hence infections can be prevented.

Dengue: There were 2.37% cases of dengue. Alam et al [6] found dengue in 24 % cases. The variation in percentage is because of geographical variation of dengue at different places. All the cases of dengue were confirmed by serological tests. Dengue causes thrombocytopenia by non-immune platelet destruction [13]. The cases of dengue had platelet count less than 50,000/cmm and presented as bleeding manifestation in the form of petechiae and purpura.

Anaemia was the next common cause contributing to thrombocytopenia accounting for 26.48% of the cases. It was not comparable to Alam et al [6] study where the anemia contributed to 8.2% of the cases. Ross et al [14] found anemia as the leading cause contributing to thrombocytopenia in 38.2% cases. In this study, anaemia was found to be the second common cause leading to thrombocytopenia. The reason for increase in number of patients in this group is that 80% of the population coming to our hospital are from village and of low socio-economic status, thus nutritional deficiency is common.

Myelosuppressants comprised cases of thrombocytopenia in 3.95% of the total; it was not comparable to Alam et al [6] who found it in 0.8% cases. Obstetric causes comprised 3.56% of the total cases in our study which was in concordance with Alam et al study who found obstetric causes leading to thrombocytopenia in 3.4 % cases.

Alcoholism was present in 3.95% cases. There are about 80% of population in the villages around Rourkela who are tribal and consume raw liquor from childhood. In these patients, the liver function tests were done and they were found to be de-ranged. There was no feature suggestive of cirrhosis. Ethyl alcohol is reported as an independent risk factor for thrombocytopenia, and it causes thrombocytopenia by a direct toxic effect on the marrow [15, 16].

We had 3.56% cases which included pregnancy induced hypertension, eclampsia and abruption placenta. Alam et al [6] reported pregnancy induced hypertension in 3.6% of the cases which was in concordance with our study. Preeclampsia is a common cause of thrombocytopenia in pregnancy and causes thrombocytopenia by increased platelet destruction. Progressive isolated thrombocytopenia in third trimester of pregnancy should raise the possibility of pregnancy induced hypertension even in absence of hypertension and proteinuria.

Snake bite was found in 3.16% cases of thrombocytopenia. Snake bite was not reported in any of the two comprehensive studies. Our hospital caters population where farming is a major occupation, and it exposes the patient to snakes. Snake bite causes thrombocytopenia as a result of direct toxic effect of the venom on the circulating platelet or as a consequence of intravascular coagulation [17].

Various hematological malignancies are known to cause thrombocytopenia, namely acute leukemias chronic leukemias like chronic lymphocytic leukemia, chronic myeloid leukemia in accelerated phase and in blast crisis, multiple myeloma. In our study hematological malignancies comprised 2.8% of thrombocytopenia.

ITP was present in 0.39% cases. Alam et al found ITP in 5.8% cases. Ross et al found ITP in 10.9% of thrombocytopenic patients. ITP causes thrombocytopenia by premature platelet destruction as a result of immune mediated mechanism.

There was a single case of DIC 0.39% presenting with multiorgan failure. In this case of twenty-five-year female with abruptio placenta and intra uterine death, mechanism of thrombocytopenia is by pathologic perturbation of a physiologic process which produces thrombosis particularly in the microcirculation. This accounts for the inappropriate deposition of fibrin and platelets in the microcirculation, with subsequent organ ischemia resulting in the characteristic hypofibrinogenemia and thrombocytopenia seen in the circulating blood. Alam et al [6] reported DIC in 0.8% of cases.

We divided thrombocytopenia cases into four groups, which were Group I: 1-1.5 lakh/cmm, Group II: 50,000 to <1 lakh/cumm, Group III: 20,000 to <50,000/cumm and Group IV: <20,000/cumm [18,19]. The majority of the cases i.e. 38.7% were in group II. Anaemia, Infections, Use of myelosuppressants, snake bite, Miscellaneous causes were not significantly associated with the decrease in platelet count. However, the hematological malignancies were found to be significantly associated with the decrease in platelet count in our study. Bleeding was found to occur in 7.90% cases, the maximum number of cases of bleeding presented in form of petechiae and purpura. The next common presentation was G.I.T bleeding in form of hematemesis or per rectal bleeding which could be explained in alcoholic patients with portal hypertension with esophageal varices.

We found a strong association between the decrease in platelet count and the percentage of cases with bleeding manifestation. Though it may be possible that just the decrease in platelet count may not have led to bleeding, additional factors like alterations in platelet function, vascular endothelial damage and acquired coagulation defects are additional factors responsible for bleeding. Gaydos et al in their study 1n 1962 demonstrated a linear relationship between platelet count and bleeding [20, 21].

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