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Clinico-Hematological Study of Pancytopenia with Special Reference to Idiopathic Pancytopenia

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Abstract

Background: Pancytopenia may present with different clinical scenario in daily practice. The present study was carried out to find the various causes of pancytopenia in Varanasi and adjoining areas with special reference to Idiopathic pancytopenia. Material Method: It was a prospective study conducted over a period of one year (Jan 2014-February 2015) at Department of Pathology in Institute of Medical sciences, Banaras Hindu University, Varanasi. Patients presenting with pancytopenia were included in the study. A provisional diagnosis was made on the clinical findings. Extensive laboratory work up (including LFT, RFT, Serology etc) was carried out to find the cause of pancytopenia in all the patients. Bone marrow aspiration was done in all the cases as a routine procedure. Bone marrow biopsy was done in 48 cases where indicated. Result: A total of 140 patients presented with pancytopenia. Among the causes, Aplastic anemia was the most common cause (31.4

Index terms— pancytopenia, aplastic anemia, myelodysplastic syndrome(MDS), idiopathic pancytopenia, idiopathic cytopenia of undetermined significance(ICUS).

Among the causes, Aplastic anemia was the most common cause (31.4%) followed by Megaloblastic anemia (22.1%) The third common cause was Myelodysplastic syndrome (MDS) (12.9%) followed by Acute leukemia (11.4%). Other causes were hypersplenism (4.3%), kala azar (2.1%), drug induced (2.1%), two cases each of HIV (1.4%), myelofibrosis (1.4%), lymphoma (1.4%) & multiple myeloma (1.4%). One case each of ITP (0.7%), SLE (0.7%) and Fanconi anemia (0.7%). Idiopathic pancytopenia constituted 5% (7 cases) of the total. On follow up of patients with idiopathic pancytopenia at 6 months, all the seven patients were having persistent pancytopenia. They were labeled as ICUS (Idiopathic cytopenia of undetermined significance (ICUS)). One patient was hospitalized with complains of generalized body weakness and few episodes of malena. Thorough work up was done to look for any cause of pancytopenia but no cause was identified and patient died due to complication of pancytopenia (due to hemorrhagic shock) in one month course and hence "Idiopathic fatal pancytopenia" term was coined for the patient. Remaining six patients were followed up at 12 months, 03 patients were having persisting pancytopenia without any specific complaints and remaining 03 patients died, for which cause is unknown. Conclusion: Pancytopenia is a common haematological problem encountered in clinical practice.The natural history of patients with ICUS is largely unknown and appears to be highly variable. ICUS patients require long term follow up to assess the evolution. "Idiopathic fatal pancytopenia (IFP)" is an emerging new entity with a grave prognosis. Further research may elucidate the underlying pathology & potential drugs to halt the inevitable fatal outcome.

1 I. Introduction

ancytopenia is the simultaneous occurence of anemia, leucopenia and thrombocytopenia. Many disease processes involve the bone marrow primarily or secondarily resulting in pancytopenia. Pancytopenia can develop due to decrease in hematopoietic cell production as a result of destruction of marrow tissue by toxins, suppression of normal marrow growth and differentiation or due to replacement of bone marrow by abnormal or malignant tissue.

The marrow may be hypocellular or hypercellular. Bone marrow examination usually provides the diagnosis in these cases. Few cases where exact diagnosis could not be made even after an exhaustive work up, these cases were regarded as Idiopathic pancytopenia. We followed up these cases at 6 month and 12 month. We particularly emphasized on these cases with the comparative study with other diagnosis. No study undertaken in this regard in India yet.

2 II. Material and Method

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The present study was a prospective study. A total of 140 patients presenting with pancytopenia were enrolled in the study. Approval from Ethical Committee and patient consent were taken. These 140 patients were divided into two age groups : Children (<18 years) & Adult (?18 years). The inclusion criteria for pancytopenia were hemoglobin (Hb) less than 10 gm/dL, total leukocyte count (TLC) less than 4000/cumm and platelet count less than 150000/cumm. A detailed clinical history and physical examination was undertaken in all the cases. A provisional diagnosis was made on these clinical findings. Peripheral smear examination and reticulocyte count was done. Samples of bone marrow aspiration were taken from the patients admitted in the Department of Medicine and Pediatrics of Sir Sunderlal Hospital, Banaras Hindu University, Varanasi. All the patients were checked for having any major clotting disorder before undergoing any procedure. BMA was performed by the standard technique using Salah needle from the posterior iliac crest under local anesthesia with standard aseptic precautions. Leishman stain was used to stain all bone marrow smears. BM aspirate for cytogenetics was takrn into a sodium heparin tube. Excess aspirate was used to make particle clot preparations or placed in an EDTA tube for making additional smears. Special cytochemical stains were undertaken in cases of leukemia. rk-39 dipstick test was done in all cases of Kala-azar. Bone marrow biopsy was done in 48 cases where the diagnosis was doubtful on aspiration. Chromosomal breakage study was advised in a suspected case of Fanconi anemia. Immunohistochemistry (IHC) with CD34 was done on biopsy section in certain cases to enumerate the exact count of blast. We followed the algorithm presented in figure 1. The mean age of patients of Idiopathic pancytopenia was 37.6±22.7 years. There were 3 children and 4 adults. The male to female ratio was 6:1. The mean Hb (gm/dl) was 6.5±2.6(4.3-10.6), mean TLC(/cumm) was 2743±929(1100-3800), mean Platelet count (/cumm) was 39100±29260 (11000-86000) and mean MCV (fl) was 89.7±11(72-106).

In our study, 7 cases presented with pancytopenia with normocellular marrow. No signs of dysplasia or increase in blast count were noted. Bone marrow biopsy was undertaken for these patients. No bone marrow fibrosis was noted. No CD34 positive cells (blast) were seen in the bone marrow by IHC. Conventional cytogenetics was performed on bone marrow aspirate and it was normal in all the cases. These cases did not respond to Vitamin B12 and folic acid therapy. Serum biochemical parameters and coagulation profile was within normal limit.

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Autoimmune profile was conducted for these patients and was within normal limit. Radiological investigations were done to rule out any specific pathology. On follow up at 6 months all seven cases were having persistent pancytopenia. These cases were diagnosed as ICUS (idiopathic cytopenia of undetermined significance). One patient presented with generalized body weakness and few episode of malena in the past. The patient was hospitalized and further work up was started to find the cause of malena and pancytopenia. In due course, patient had declining trend in the hematological parameters and started bleeding and went into hemorrhagic shock and died. No cause of pancytopenia could be identified and hence we coined the term Idiopathic fatal pancytopenia for this patient. Remaining six patients were followed up at 12 months, 3 patients were having persistent pancytopenia and three patients died, for those the cause is not known as they were not available for any work up. The most common presenting symptom was generalized body weakness in 126 patients (90%). The most common sign was pallor in 137 cases (97.8%)

The various causes of pancytopenia were divided into five categories for further evaluation as Aplasticanemia, Megaloblastic anemia, Infiltrative disorders[including acute leukemia-myeloid(AML) and lymphoid(ALL), myelodysplastic syndrome(MDS), lymphoma, multiple myeloma], Others [including, Fanconi anemia, hypersplenism, kala-azar, HIV, septicemia, drug induced causes, SLE, myelofibrosis and immune mediated thrombocytopenic purpura(ITP)] and Unknown causes(idiopathic pancytopenia) In our study, MCV was significantly increased in cases of pancytopenia due to megaloblastic anemia (24 out of 31 cases) where as it was within normal range in other causes of pancytopenia due to aplastic anemia and infiltrative causes. The correlation between megaloblastic anemia and macrocytic anemia was found to be significant in our study with p value <0.05. Aplastic anemia and other infiltrative conditions were associated with normocytic anemia which was found to

be significant. Red cell distributon width RDW-CV was significantly increased in cases of pancytopenia due to megaloblastic anemia as compared to other causes which had normal RDW values. Mean platelet volume (MPV) was also significantly increased in cases of megaloblastic anemia as compared to other causes of pancytopenia (aplastic anemia, infiltrative lesion).

7 IV. Discussion

Pancytopenia is defined by reduction of all the three formed elements of blood below the normal reference range [1] . Pancytopenia is a common hematological finding with different clinical scenario.

In our study the male: female ratio was 1.37:1. This is in agreement with other studies shown in (table 5). The male preponderance may be partly explained by increased exposure of male to environmental agents like agricultural pesticide [2] . Few studies showed female preponderance [3,4] common sign was pallor (97.8%) comparable to many other Indian studies (table 5).

We compared our data with various International and Indian studies on pancytopenia (table 6). The most common cause in our study was Aplastic anemia. Many International studies [5,6,7,8,9,10,11,12] and national studies [4,13,14] were in agreement with our finding as aplastic anemia as the most common cause of pancytopenia. Whereas few studies reported aplastic anemia as the second most common cause [15,16,17,18,19,20,22] . Significant lymphocytosis was associated with aplastic anemia compared to other causes of pancytopenia. This finding was in agreement with SomaYadav et al., The pathophysiology of Aplastic anemia is believed to be immune mediated, with active destruction of blood forming cells by the lymphocytes . [4] Megaloblastic anemia was the 2 nd common cause in our study whereas few Indian studies [18,19,20,21,22,23,24,25] and international studies [16,34] reported it as the first common cause. This may be due to the fact that ours is a tertiary care centre where many referral cases come which might have been treated with hematinic therapy previously.

Out of 31 cases of Megaloblastic anemia, 26 had elevated LDH levels. All the cases improved with Vitamin B12 and folic acid therapy. R Para et al., and Evazi-ziaei et al., also observed increased LDH in megaloblastic anemia [25,26] . Lactate dehydrogenase enzymes is released during the The expected increase in LDH activity is the result of an accelerated turnover of bone marrow cells implying release of this enzyme from dividing or decaying cells. [27] In MDS, most of the patients (75%) were under the age 50years and 27% of cases were below 20 years. Usually MDS is considered to be disease of elderly, but in the Indian series by S Nigam and Sudha Rani et al.,overall 75.5% of individual (20/33) were of <50 years of age, 8 (21.6%) of 33 patients were less than 20 years of age [28] . This may be due to the fact that the incidence of MDS appears to be increasing over the past decade due to recognition of the syndrome by the physician and hematopathologist.

Acute leukemia is the 3 rd common cause in our study. Many Indian studies are in agreement with ours study. Sarod R etal., reported acute leukemia as the 2 nd common cause. [29] Various International studies reported few cases of pancytopenia with normal bone marrow (refer table 6). The frequency varies from 3.38% to 10.5%. No follow up was mentioned in them. No study has reported the phenomenon of Idiopathic pancytopenia. In our study we reported 5% of these cases (pancytopenia with normal marrow and normal karyotype). We followed up these cases at 6 months and 12 months.

ICUS is a recently proposed, provisional diagnostic category that recognizes patients who present with cytopenias of undetermined etiology [30,31] . The proposed criteria for diagnosing ICUS [30] : a) Persistent cytopenia (for 6 months): hemoglobin <11 g/dl, neutrophils <1.5×109L, and platelets <100×109/L; b) No morphologic features of myelodysplasia c) Normal chromosome analysis and d) A detailed clinical history and investigation that excludes other secondary causes of cytopenias. The natural history of patients with ICUS is largely unknown and appears to be highly variable [32] . Small studies indicate that some patients will go on to develop frank MDS or a related myeloid malignancy such as AML [33] . Others may follow a more indolent course [34] . ICUS cases require long term follow up to assess the evolution. In our study, all the seven cases fulfilled the criteria for ICUS. One patient was hospitalized for an extensive work up but within one month patient died due to hemorrhagic shock and no cause could be identified. The course of the patient was fatal and hence the patient was termed as Idiopathic fatal pancytopenia. Out of remaining six patients on follow up at 12 months, three patients were having persistent pancytopenia and another three patients were expired due to unknown cause. Hence the course of ICUS in our study was variable.

The incidence of hypersplenism was 4.3%. All cases were caused by portal hypertension secondary to liver cirrhosis. The incidence of pancytopenia caused by hypersplenism among international studies varied from 0 % to 19% [14,29] as well as among Indian studies varied from 0 %-11.5%. Our incidence of 4.3% was within the range reported by various workers.

Other infections included Septicemia and HIV. The incidence was 2.1% in our study. There was a single case of septicemia presenting as pancytopenia in children. Two cases of HIV in adults were reported. The incidence of septicemia in various studies varied from 1.6% to 17.2% [4,19,25,35] and our data was within the aforementioned range.

There was a single case of ITP in a 17 year old female with fever, pallor and petechial rashes. The incidence of ITP in our study was 0.7%. In other studies, the incidence varied from 1.7-7.8%. [23,25,13] We also compared our data with various studies in children (table 7). Overall in adult(51.1%) and children (58.4%), aplastic anemia and megaloblastic anemia were the two most common causes of pancytopenia in our study.

MCV, RDW-CV & MPV was significantly increased in cases of pancytopenia due to megaloblastic anemia

where as it was within normal range in other causes of pancytopenia due to aplastic anemia and infiltrative causes. Soma Yadav et al., & Gupta et al., also assessed the role of MCV, RDW, MPV in cases of pancytopenia and they are in agreement with our study. [4,38] V. Conclusion

Pancytopenia is a common hematological problem encountered in clinical practice. The most common cause of pancytopenia is Aplastic anemia followed by Megaloblastic anemia.ICUS cases require long term follow up. "Idiopathic fatal pancytopenia (IFP)" is an emerging new entity with a grave prognosis. We wish to sensitize the medical community & the scientists to this rapidly fatal condition of unknown etiology.Further research may elucidate the underlying pathology & potential drugs to halt the inevitable fatal outcome. [1] [2] [3] [4] [5]

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Figure 1: Table 1 :

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Case no	Age	Sex	Hb(gm%)	TLC(/Ul)	Platelet(/cumm)	MCV(fl)	%Blast in PBS*	%blast in BM	BM** cellularity	BM fibrosis	CD34on BM cells	Cytog
1	60	M	4.3	1100	13000	72	0	0	NC***	No	0	46,XY
2	17	F	4.9	3100	39000	84.1	0	0	NC	No	0	46,XX
3	65	M	4.5	2200	11000	106	0	0	NC	No	0	46,XY
4	11	M	10.6	2700	84000	90	0	0	NC	No	0	46,XY
5	17	M	4.4	2600	75000	90	0	0	NC	No	0	46,XY
6	55	M	9.5	3700	29000	86.2	0	0	NC	No	0	46,XY
7	38	M	7.4	3800	23000	100	0	0	NC	No	0	46,XY

*[Note: *PBS -peripheral blood smear, **BM-bone marrow, ***NC-normocellular]*

Figure 2: Table 2 :

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Symptoms & signs	Number of patients (out of 140)	Percentage %
Generalized body weakness	126	90
Pallor	137	97.8
Fever	86	61.4
Bleeding	57	40.7
Splenomegaly	26	18.6
Hepatomegaly	16	11.4
Lymph node	15	10.7
Pedal edema	10	7.14

Figure 3: Table 3 :

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Diagnosis	MCV(fl) Chi square(DF=8) 55.78 P value <0.05			RDW-CV (%) Chi square(DF=	
	< 83fl	83-99fl	>99fl	11.6-14%	>14%
Aplastic anemia	3	34	7	31	13
Megaloblastic anemia	4	3	24	2	29
Infiltrative disorders	7	22	9	14	24
Others	8	11	1	8	12
Unknown cause	1	4	2	3	4
Number of cases	23	74	43	58	82

Figure 4: Table 4 :

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Study	Age group	M:F ratio	Most common presentation	Most common sign
Deepak B.Kr et al., 3	10-70yr	1.0:1.8	Generalisedweakness (70.83%)	Pallor (45.83%)
Soma Yadav et al., 4	All ages, <30yr-73.3%	1:1.2	Fever	Pallor
JigneshKumar et al., 21	1-95yr	1.6:1	Easy fatigability (79%)	Pallor (100%)
Nigam RK et al., 22	2-80yr	1.12:1	Generalized weakness, fever	Pallor , splenomegaly
BhaskarBThakkar et al., 23	13-86yr	1.08:1	Generalisedweakness (97%) and fever (70%)	Pallor (100%)
A Chhabra et al., 24	6month -14yr	-	Bleeding manifestation (70.3%) Fever (63.7%)	Pallor (64.8%)
Rajesh Para &Shailajapara et al., 25	3-90 yr	1.1:1	Generalized weakness (51.7%)	Pallor (25.9%)
ArvindJain et al., 39	2month-95yr	2.6:1	-	-
Present study	1-72yr	1.37:1	Generalisedweakness (90%)	Pallor (97.8%)

Figure 5: Table 5 :

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Study	Country
International agranulocytosis and aplastic anemia study 5	Israel Europe 1987
Keisu M and Ost A et al., 15	Israel Europe 1990
Hossain MA et al., 6	Bangladesh1992
David Savage G, 16	Zimbabwe 1997
Mussarrat Niazi Fazl-i-Razig7	Pakistan 2000
Ishtiaq O Bagai HZ40	Pakistan 2001
Khudairabbas et al., 17	Iraq 2004

Volume XVII Issue I Version I Jha et al.,8 Lakhey et al., 9 Nepal 2010 Nepal 2008 Tajali khan et al.,10 Pakistan 2011 Pudasaini et al.

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Study	Country	Number of cases	AGE	Most common cause	2 nd Most common cause	3 c c
Gupta V et al.,36	India 2008	105	1.5-18yr	Aplastic anemia (43.8%)	Acute leukemia (25.7%)	Ka
Chabbara A et al.,24	India 2012	111	6 month -14 yr	Megaloblastic anemia (31.8%)	Malignancies (25.2%)	Infec
Jan AZ et al.,11	Pakistan 2013	205	6 month-14 year	Aplastic anemia (28.3%)	Hematological malignancies (25.2%)	M a (
Pathak et al.,12	Nepal 2013	6(out of 48)	<15yr	Hypoplastic anemia (3cases)	Hematological malignancies (2 cases)	M a c
Present Study	India 2015	48(out of 140)	<18yr	Aplastic anemia (41.7%)	(16.7%) Megaloblastic anemia	A le (M

Figure 7: Table 7 :

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[2]© 2017 Global Journals Inc. (US)
[3]© 2017 Global Journals Inc. (US)Year 2017
[4]© 2017 Global Journals Inc. (US)Year 2017
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Vijai Tilak, Raini Jain 18 India 1999 77 Megaloblastic anemia (68%) Aplastic anemia (7.7%)

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