Original article

Clinicohematological evaluation of splenomegaly

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Abstract:

Background: Splenomegaly is a subject of considerable clinical concern in a symptomatic patient and warrants thorough clinical and laboratory evaluation. Present study was attempted to study cases of splenomegaly with special reference to etiological classification, hematological profile and frequency of hypersplenism associated with it.

Materials and Methods: Eighty patients referred for hematological work with the primary diagnosis of splenomegaly were studied with clinical evaluation & hematological investigations. These included peripheral blood smear, reticulocyte count, automated cell counts by cell counter, bone marrow aspiration or biopsy and other pertinent hematological investigations.

Result: The age range was 14 to 65 years, Male: Female ratio was 1.6:1. On etiological classification of splenomegaly, various hematological disorders were seen 34 cases, lymphoreticular malignancies in 22 cases, congestive splenomegaly in 13 cases, infective disorders in 6 cases and systemic lupus erythematosus in one case. Four cases remained undetermined. Hypersplenism was seen in 28 cases. Commonest cause of hypersplenism was congestive splenomegaly. Grade I splenomegaly was seen in 17 cases, Grade II in 34cases, Grade III in 19cases and Grade IV in 10 cases.

Conclusion: There was no significant correlation between degree of splenomegaly and degree of cytopenia. Increasing splenic size was significantly associated with occurrence of hypersplenism.

Keywords: Splenomegaly, Hypersplenism, Hematological investigations

Introduction:

Palpable spleen in a symptomatic person is always significant. Splenomegaly is a subject of considerable clinical concern as spleen is not normally palpable. When palpable, it may be associated with serious disorders including hematological malignancies from which no age group is exempted. A wide variety of diseases can lead to splenic enlargement. The predominant causes of splenomegaly vary with geographical distribution of diseases prevalent in the area.[1, 2] Present study of splenomegaly in a general purpose tertiary care government hospital is a humble attempt to elucidate its etiopathogenesis and associated hematological manifestations.

Materials & methods:

Present observational study of splenomegaly was done in Department of Pathology in a tertiary care government hospital in collaboration with Department of Medicine. The study was carried out during the period of one and half year. It included prospectively registered cases of splenomegaly admitted in the hospital and referred to hematology laboratory for hematological work up including bone marrow examination. We excluded pediatric patients as spectrum of splenomegaly in them is different. After seeking approval of institutional ethics committee and taking informed consent, 80 such cases were enrolled in the study. Clinical presentation of splenomegaly was studied (table1)

The patients were evaluated clinically for grading and etiology of splenomegaly. (table 2) These patients were then subjected to profile of investigations which included peripheral blood smear, automated cell count on Sysmex 18 parameters, 3 part cell counter-K4500, and other pertinent hematological investigations like sickling test, osmotic fragility test etc, and bone marrow examination (aspiration and / or biopsy). Splenectomy was done in six cases. Hematological investigations were repeated after seven days of splenectomy. Examination of splenectomy specimens was carried out for gross and microscopic appearance.

The data collected was analysed to find out etiology of splenomegaly and its hematological manifestations including those of hypersplenism. An attempt was made to correlate degree of splenomegaly with degree of anemia and cytopenia by applying Chi Square test in cases of hypersplenism. Similarly attempt was made to find out statistical association of increasing size of the spleen with hypersplenism by applying Chi square test.

Grading of splenomegaly was done by Hackett's classification. [3] Hackett's classes 1 and 2 were considered as mild splenomegaly, class 3 as moderate splenomegaly and classes 4 and 5 as massive splenomegaly. Hypersplenism was diagnosed on the basis of study of peripheral blood and bone marrow. The criteria to diagnose hypersplenism in patients with splenomegaly included a peripheral blood picture of anemia, neutropenia and thrombocytopenia either singly or in combination with a cellular bone marrow picture. [4]

Results:

Age and sex incidence of splenomegaly: Study group included 50 males and 30 females. There were 7 adolescent patients and 73 adults. The age range was 14 years to 65 years.

Table 1: Clinical presentation of splenomegaly

Clinical presentation$	No. of cases
Fever	25
Tenderness#	3
Association with hepatomegaly*	40
Association with lymphadenopathy**	16
Hepatomegaly with lymphadenopathy***	12
Seropositive for HIV****	8

There was symptomatic overlap in some of the cases. Tenderness was noted in 3 cases with Grade II to III splenomegaly. These included one case each of prolymphocytic leukemia, splenic vein thrombosis and liver cirrhosis with severe anemia. Associated hepatomegaly was a feature seen in 24 cases of anemia, 14 cases of myelo & lymphoproliferative disorder, 4 cases each of infections and congestive splenomegaly, Two cases of plasma cell dyscrasia and one cases each of SLE and undetermined splenomegaly.* Splenomegaly with lymphadenopathy was seen in 13 cases of lympho and myloproliferative disorder and 3 cases of plasma cell dyscrasia.** The triad of splenomegaly, hepatomegaly and lymphadenopathy was noted in 8 cases of lymphoproliferative disorder, 2 cases of plasma cell dyscrasia and one case each of megaloblastic anemia, tuberculosis.*** Four cases of dimorphic anemia, 2 cases of undetermined splenomegaly, one case each of liver cirrhosis and tuberculosis were sero- reactive for Human Immunodeficiency Virus.(HIV) ****

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Ultrasonographic features of splenomegaly: The clinical assessment of grading correlated with ultrasonographic features in all these cases. Specific ultrasonographic findings were seen in 6 cases. Multiple small hypoechoeic lesions of microabscesses were seen in one case each of septicemia, megaloblastic anemia with cardiac failure, HIV and systemic lupus erythematosus (SLE). Multiple focal hypoechoeic lesions were noted in one case of nonhodgkins lymphoma (NHL). Heterogenous enlargement was seen in case of primary splenic lymphoma.

Table 2: Etiological classification, grading of splenomegaly & association with hypersplenism

Etiology	**Grade**						**Hypersplenism**
	I (n)	**II (n)**	**III (n)**	**IV (n)**	**TOTAL**	**%**	**n**
A] Hematological					**56**	**70**	**7**
Anemia	12	15	3	o	30	38.89	5
Polycythemia vera				1	1	1.11	
Myelofibrosis			2	1	3	3.33	
Leukemia	2	4	2	5	12	17.78	1
Plasma cell dyscrasia	1	2			3	3.33	
Lymphoma		1	4	1	6	7.78	1
B] Non-Hematological					**20**	**25**	**17**
Infections	1	2	2	1	6	6.67	2
SLE		1			1	1.11	1
Congestive		8	5		13	14.44	10
C] Undetermined	1	1	1	1	**4**	**5**	**4**
TOTAL	**17**	**34**	**19**	**10**	**80**	**100**	**28**

Infections included one case each of septicemia, malaria, tuberculosis and kala azar and two cases of HIV. On critical evaluation it was found that in 8 cases, splenomegaly involved multiple factors.

Hypersplenism: On critical clinico-hematological evaluation it was found that element of Hypersplenism was present in 28 cases. (table3) There was statistically significant association between increasing size of spleen and occurrence of Hypersplenism (P< 0.005).

Table 3: Etiology & Grading of splenomegaly in hypersplenism

Etiology	**Grading Of Splenomegaly in hypersplenism**				
	I	II	III	IV	Total
Kala azar				1	1
Septicemia		1			1
SLE		1			1
Liver cirrhosis		2	5		7
Portal vein thrombosis			2		2
Splenic Vein thrombosis		1			1
Undetermined		1	2	1	4
Iron deficiency anemia	2	1			3
Dimorphic anemia			1		1
Autoimmune hemolytic anemia			1		1
Hairy cell leukemia			1		1
Primary splenic lymphoma				1	1
Total	3	8	12	5	28

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Table 4: hematological findings in cases of hypersplenism

Parameter	**Grading of splenomegaly**				
	I(n-3)	II(n-8)	III(n-12)	IV(n-5)	TOTAL
Hb (gm %)					
>9to11	1	1	4	2	08
>5 to 9		4	4		08
<5	2	3	4	3	12
T L C (/cmm)					
Normal	1	1	3	2	07
>3000 to 4000	1	2	3		06
>2000 to 3000	1	3	2	2	08
>1000 to 2000		2	4	1	07
Platelet count (/cmm)					
Normal		1			01
>1,00,000- to 1,50,000			1	3	04
>50000 to 1,00,000	1	1	5	1	08
<50000	2	6	6	1	15
Bone marrow findings	I	II	III	IV	TOTAL
Cellularity					
Normocellular	1				1
Hypercellular	2	7	12	4	25
Erythroid Series					
Normocellular	1				1
Hypercellular	2	7	12	4	25
Myeloid Series					
Normocellular	1		4	1	6
Hypercellular	2	7	8	3	20
Megakaryocytes					
Increased	3	7	12	4	26

Hematological findings in cases with hypersplenism (Table4)

All cases had anemia which was moderate to severe with Hb less than 9 gm% in 20 cases (74.42 %). In about half of the cases (n=15, 53.57 %) leucopenia was moderate to severe with total Leucocyte Count /cmm less than 3000 and thrombocytopenia was severe with platelet count less than 50000/cmm.On attempting correlation between grading of splenomegaly and degree of anemia and cytopenia with cut of values of Hb less than 5 gm/dl, TLC <3000/cmm and platelet count <50,000/cmm, following observations were noted. There was no correlation between degree of splenomegaly and degree of anemia and cytopenia (P> 0.05) There was significant association between increasing size of spleen and occurrence of Hypersplenism (P< 0.005).

Hematological findings in non-hematological conditions (n:20) and undetermined splenomegaly (n:4) The feature of hypersplenism was seen in 17 out of 24 such cases (70.83%). The hematological changes related to hypersplenism were as follows. Pancytopenia was noted in total of 5 cases (4 cases of liver cirrhosis and one case of undetermined splenomegaly). Anemia and thrombocytopenia were seen in one case each of congestive splenomegaly and undetermined splenomegaly. Anemia alone was noted in remaining 10 cases. Bone marrow was

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hypercellular in all cases of hypersplenism and normocellular in remaining 7 cases. (One case each of malaria & tuberculosis, 2 cases of HIV, 3 cases of liver cirrhosis).

Bone marrow iron was normal in 10 cases (5 cases of congestive and 4 cases of undetermined splenomegaly & one case of SLE). It was increased in 3 cases of congestive splenomegaly and decreased in 8 cases (5 cases of congestive and 2cases of undetermined splenomegaly & one case of infection) The granuloma was noted in one case of tuberculosis.(fig1b) One case each of malaria and kala azar(fig1a) showed these parasites in bone marrow. **Hematological profile of hematological conditions with splenomegaly:**Besides usual features of these hematological conditions element of hypersplenism was noted in 8 cases of anemia (Iron deficiency:3, Hereditary spherocytosis: 2 , one case each of dimorphic and auto immune hemolytic anemia and thalassemia) and one case each of, Hairy cell leukemia and primary splenic lymphoma.Bone marrow findings in hematological conditions can be summarized as follows.

Bone marrow was hypercellular in 59 cases, normocellular in 6 cases and hypocellular in one case of NHL. Serum Iron was decreased in 34cases, normal in16 cases and increased in 14 cases. Neoplastic cell infiltration was noted in 23 cases (fig1d)

(Leukemia: 15, Lymphoma: 5, Plasma cell dyscrasia: 3 cases). There were 3 cases of myelofibrosis.

Hematological findings provided a clue for the etiology of splenomegaly in 69 cases (76.66%). These included all cases with hematological diseases except one case of primary splenic lymphoma which was diagnosed on examination of splenectomy specimen and 4 cases of infection namely Septicemia, Malaria, Leishmaniasis and Tuberculosis with granuloma in bone marrow with one cases each.**Splenectomy**: Splenectomy was done in three cases of hypersplenism. The indications included undetermined splenomegaly 2 cases and congestive splenomegaly due to liver cirrhosis in one case. One case of undetermined splenomegaly could be diagnosed as primary splenic lymphoma after splenectomy.(fig1c)On morphological examination thickened capsule and Gandy Gamna bodies were seen in case of congestive splenomegaly. Activated white pulp was seen in congestive and undetermined splenomegaly. A case of splenic lymphoma was diagnosed solely on splenectomy which revealed nodular deposits of low grade NHL in white pulp.

Post splenectomy hematological profile: Reversion of Hypersplenism with normalization or improvement in hematological parameters was noticed in all cases of splenectomy. Peripheral blood smear revealed target cells.

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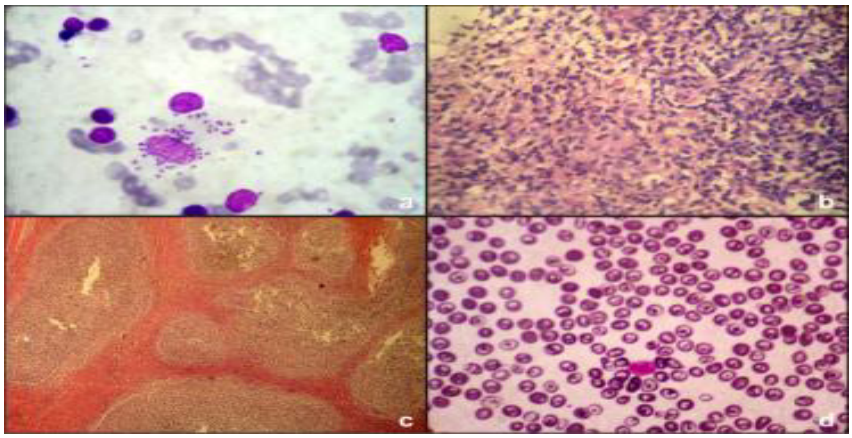

Figure1a: BM aspiration showing Leishmania donovani parasites,(Leishman, 1000X).

Figure1b: BM biopsy showing tuberculous granuloma,(H &E,400X)

Figure1c: Primary splenic lymphoma, (H&E,X)

Figure1d: Post splenectomy Peripheral blood smear showing target cells(Leishman,400X)

Discussion:

Splenomegaly in a symptomatic patient is of considerable clinical significance. One must investigate a case of splenomegaly as many of the conditions causing splenomegaly are treatable.[2]This is exemplified in three of our cases of splenectomy which showed normalization or improvement of hematological picture. The experience is shared by Sunderesan et al.[5] As also the cases of nutritional anemia and infections can also be treated with medical line of treatment. Nadim et al have shown regression in splenic size with correction of iron deficiency.[2] In present series we have come across 3 cases of iron deficiency anemia which had shown features of hypersplenism.

Given the multitude of functions of spleen, it is not surprising that splenomegaly occurs in variety of conditions. However careful clinical evaluation and routine hematological investigations provide answers in of many of these conditions. This is exemplified in observations in present study which showed very few cases of infective pathology. We have come across only one case of malarial infection with a very low density parasitemia missed on peripheral blood smear, while there were 96 cases of malaria admitted during study period. The extensive hematological work up was done in this case and bone marrow study and the malarial parasites were picked up in bone marrow examination. Similarly cases of enteric fever, or septicemia which had splenomegaly were diagnosed by other pertinent investigations and were not referred for hematological work up. Incidentally we have evaluated only those cases of splenomegaly which were referred to us by clinicians for extensive hematological workup, especially bone marrow examination. This also explains paucity of hemolytic anemia in present study sample, which can be attributed to the fact that hemolytic anemia can be readily diagnosed on clinical grounds and pertinent investigations and hence were not referred as primary cases of splenomegaly to us by clinicians.

The significance of hematological investigations in cases of splenomegaly is multidimensional. On one hand hematological conditions (73.33% in present study) are the frequent cause of splenomegaly and on the other hand an enlarged overworking spleen results in cytopenias which need to be investigated with hematological tests. Routine hematological

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evaluations may provide an important clue about the etiology of splenomegaly, for example, finding a parasite, evidence of hemolysis, septicemia, leukemia, lymphoma or myeloma spillover on peripheral blood smear resolves a mystery of splenomegaly. Bone marrow is a key investigation in study of splenomegaly. In present study, we had 5 cases of subleukemic leukemia with splenomegaly which were diagnosed on bone marrow examination. Similarly the only case of malaria referred for hematological work up of splenomegaly, case of leishmaniasis and a case of tuberculosis were diagnosed only on bone marrow examination. In a case of hairy cell leukemia and in cases of lymphoma and myelofibrosis, bone marrow was the important diagnostic investigation. Ali et al have discussed in detail importance of bone marrow examination in evaluation of splenomegaly.[1]

The most frequent cause of splenomegaly in present study was hematological diseases followed by congestive splenomegaly(associated with liver cirrhosis). The experience is shared by O Reilly, while most of the other studies showed infection as second leading cause of splenomegaly. [1,2,6]

Amongst the Hematological disorders frequently associated with splenomegaly in present study was anemia. Interestingly most of these were nutritional anemias. Not all these cases exhibited features of congestive cardiac failure(CCF), thereby suggesting some other mechanism for splenomegaly. Next frequent group of hematological disorders was leukemia and lymphoma. As the study sample included only those cases which could not be primafacie attributed to definitive etiology of splenomegaly, the picture may not be realistic. This is reflected in inclusion of only few cases of chronic myeloid leukemia, though chronic myeloid leukemia is the most frequent hematological condition associated with splenomegaly. Interestingly, one case of primary splenic lymphoma was diagnosed after splenectomy. Splenomegaly is an important manifestation of myelofibrosis and polycythemia vera which were found in three cases and one case respectively. In non-hematological group, infection was found to be a causative factor in 6 cases. We have attributed definitive and specific infections which were sole cause of splenomegaly to this group. Interestingly additional possible systemic infections were picked on USG finding of micro abscesses in 3 more cases including one case of HIV infection. Thus USG examination broadened our perspective on possibilities of etiology. Experience is shared by others.[7] Seven more cases were sero-reactive for HIV but had some other reasons for splenomegaly and hence were classified under those conditions. In present study splenomegaly associated with liver diseases, portal and splenic vein thrombosis was classified under the heading of congestive splenomegaly and formed second most cause frequent cause of splenomegaly in nonhematological group.Despite very careful analysis, one of our case of splenomegaly with severe normocytic normochromic anemia remained undetermined even after splenectomy which showed mild activation of white pulp. The case was associated with hypersplenism and showed normalization of hematological parameters on splenectomy.

We have not offered a diagnosis of tropical splenomegaly to 3 remaining cases of undetermined splenomegaly in our series as we could not elicit history of malaria in the past and we have not done immunological investigations for malaria.Tender splenomegaly was a rare feature in present study only to be seen in one case of massive enlargement in

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prolymphocytic leukemia & 2 cases of congestive splenomegaly, one of which had splenic vein thrombosis. We found 27.7% of our cases to be associated with CCF. It is not a frequent cause of splenomegaly according to some authors.[8] Besides clinical grading, splenomegaly can also be graded on imaging. In present study it was done with USG and results were comparable. Recently thresholds for recognizing and grading the splenomegaly from volumetric assessment on CT scan are introduced which are shown to match well with clinical assessment.[9]

Occurrence of multiple organ enlargement is an important feature of infections and myeloproliferative and lymphoproliferative disorders and plasma cell dyscrasia.. This consideration should help in clinical decision of etiology of splenomegaly.

There were 5 cases of subleukemic leukemia where splenomegaly acted as an important indicator of the disease process in presence of very few blasts on peripheral blood smear.

In present study megaloblastic anemia was seen in 11 cases, which showed mild to moderate splenomegaly. In 4 cases it was due to CCF, while in rest, it may be attributed to some unknown mechanism of hemolysis antecedent to megaloblastic anemia. In present series hypersplenism was found in 31.11% cases. The splenic enlargement noted in these cases was predominantly moderate to severe and congestive splenomegaly was the frequent cause of hypersplenism. Congestive splenomegaly predominated (n: 10, 35.7%) in this group followed by anemia (n:8,28.57%). Experience is shared by others who have shown liver diseases to be the important cause of hypersplenism.[6,8] Moderate to severe degree anemia was a feature of 71.42% cases (n:20) while severe degree leucopenia and thrombocytopenia was seen in 25 % (n:07) and 53.57% cases (n:15) respectively in hypersplenism in present study. There was statistically significant association between increasing size of spleen & hypersplenism. However there was no correlation between splenic size & degree of anemia and cytopenia. The experience is shared by others[5]. Splenectomy performed in 3 cases was rewarding in terms of sole means of diagnosis of primary splenic lymphoma and normalization of blood picture in all cases. On the whole, our study emphasized importance of extensive hematological workup including bone marrow studies in cases of splenomegaly which could not be easily resolved on clinical grounds.

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