Bone Marrow Reticulin Content In Acute Leukemia

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Summary:

Background: *Increase in marrow reticulin has long been recognized in primary myelofibrosis, but little was known about the reticulin structure of leukemic marrows, there has been a tendency to accept an increase in marrow reticulin as evidence of myelofibrosis. Similarly, there has been a tendency to diagnose as "acute myelofibrosis" cases of acute leukemia with brisk reticulin and early collagen production. This study was undertaken to determine incidence, type and pattern of fibrosis in the bone marrow of patients with acute leukemia, both acute lymphoblastic and acute myeloid leukemia.*

Method: *thirty-five bone marrow biopsy specimens from patients with acute leukemia were examined histologically; connective tissue stains were applied for stromal studies.*

Result: *an increase in marrow reticulin is common at presentation in patients with acute leukemia, effective anti-leukemic therapy results in resolution of the increased marrow reticulin.*

Conclusion: *The reticulin type of fibrosis is the common type encountered in acute leukemia which is of diffuse pattern, higher incidence of bone marrow fibrosis in patients with acute lymphoblastic leukemia than those with acute myloid leukemia. Fiber bone formation is found in 10% of cases of acute lymphoblastic leukemia ,but is not extensive and well developed as in cases of primary myelofibrosis.*

Keywords: *acute leukemia, bone marrow biopsy, reticulin content.*

Introduction:

Reports in the literature deal almost with cytologic and cytochemical investigation, in contrast, studies on bone marrow histology in the acute leukemia have been few and far between. One structural characteristic which has received attention is the reticulin fiber content in the leukemic infiltrations. Kundel etal[1]stated that acute leukemias with an increase in reticulin fibers in the bone marrow did not respond well to chemotherapy and had a poorer life expectancy. Similarly, Manoharan etal,[2]noted that reticulin fibers decreased when the leukemia was successfully treated and reappeared with the occurrence of relapse. They offered no explanation to account for this association. Like wise only a few data are available on the prognostic value of other histologic criteria such as the proliferation patterns and the volume percentages of infiltration, hematopoiesis and fat in the bone marrow biopsy. Two histologic variables had predictive value, in addition to the cytologic cell type: the content of fat cells and the degree of fibrosis. Patients with a high content of fat cells, diffusely dispersed among the leukemic blasts(interstitial pattern), had longer survival times than those without fat cells(packed marrow pattern).An increase in reticulin fibers indicated shorter survival times. The degree of fibrosis which accompanies the acute leukemias varies widely, from mild to marked and may resemble an acute myelosclerosis. [3, 4]

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Materials And Methods:

Blood films, bone marrow aspirates and trephine biopsies of twenty patients with acute lymphoblastic leukemia [ALL] and fifteen patients with acute myloid leukemia [AML] seen in the medical city teaching hospital were examined. The initial diagnosis of acute leukemia was based on established cytologic [FAB system],cytochemical and clinical criteria. The marrows smears or imprints of the biopsies were stained with May-Grunwald-Giemsa, PAS, Sudan-Black and, if required, alpha-naphthylacetate esterase. The trephines were fixed in Bouin's solution to achieve partial decalcification and were finally embedded in paraffin prior to sectioning at a thickness of 5µ.The following staining techniques were used: routine haematoxylin and eosin, silver impregnation for reticulin and Van Gieson's stain for collagen. The histological sections from each patient were examined for leukemic infiltrate, reticulin content of the marrow and presence or absence of collagen among the reticulin fibers. The reticulin content of the marrow was graded using Bauermeister [9] scoring system.

o - No reticulin fibers demonstrable.

N - Occasional fine individual fibers only.

1+ - Occasional fine individual fibers, plus foci of fine fiber network.

2+ - Fine fiber network through out most of the section; no coarse fibers demonstrated.

3+ - Diffuse fiber network with scattered thick, coarse fibers but no true collagen {negative VanGiesin's stain}.

4+ - Diffuse, often coarse, fiber network with areas of collagenization {positive VanGiesin's stain}.

The marrow trephine biopsy findings were related to the type of acute leukemia.

Results

Table 1 shows the reticulin content in the 35 patients with acute leukemia at presentation.

Table 1. Marrow reticulin content in acute leukemia

Type of acute leukemia	Total no. Of patients	Reticulin content of marrow at presentation					
		0	N	1+	2+	3+ V.G.-	4+ V.G. +
		Normal range					
ALL L1	2					1	1
L2	16	1		1		9	5
L3	2					1	1
AML M0	-						
M1	-						
M2	6		1	1	3	1	
M3	3		1	1		1	
M4	2	1	1				
M5	3				3		
M6	-						
M7	1						1
	35	2	3	3	6	13	8

The age range of patients with ALL was 3-67 years, mean 22.7 years. 18 of the 20 patients (90%) with ALL had an increased reticulin content of the marrow initially ($p < 0.005$) which was diffuse in 17 (14 L2, 2L1, 1L3), paratrabicular pattern noticed once in L3. [Fig.1 (a, b)]. Collagen type of fibrosis encountered in 7 cases, fibrosis plus ostiomylosclerosis seen in 2 cases [Fig.2]. Dry tap occurred in 2 cases with reticulin fibrosis. Follow up of two L2 patients with fibrosis noticed revision to normal after remission. [Fig.3 (a, b, c, d)]

13-65years was the age range of AML patients with a mean of 33.7 years. Three out of fifteen (20%) had an increased marrow reticulin at presentation ($p<0.005$), the fibrosis was diffuse in all of them, reticulin type in two (one M_2 type, otherM_3 type of AML) [Fig.4 (a, b)], collagen type in one (M_7 type, pericellular pattern) [Fig. 5], dry tap zero.

Fig. (1).a. Paratrabecular location of bone marrow fibrosis patient with ALL L3. Gomori reticulin method.

.Fig.(1) b Same patient showing collagen fibrosis with a reticulin score of 4+.
Van Gieson's method for collagen fibrosis X 100.

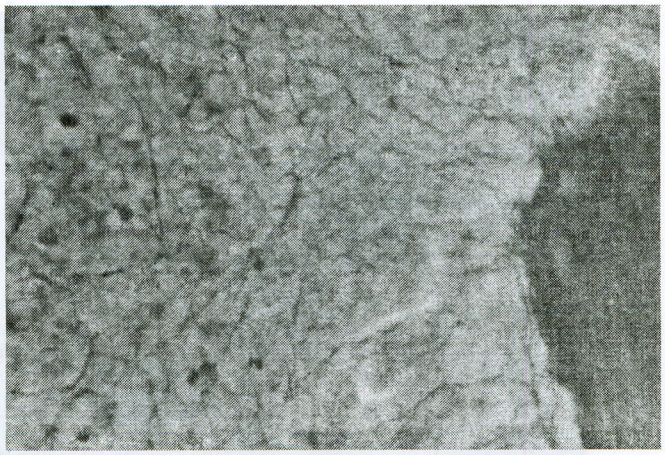

Fig (3) b. same patient showing myelofibrosis with a reticulin score of 3+, [Note the presence of coarse fibers which was not apparent in the H&E preparation]. Gomori reticulin method x100.

Fig. (2) osteomyelosclerosis in a patient with ALL. Gomori reticulin method X 100.

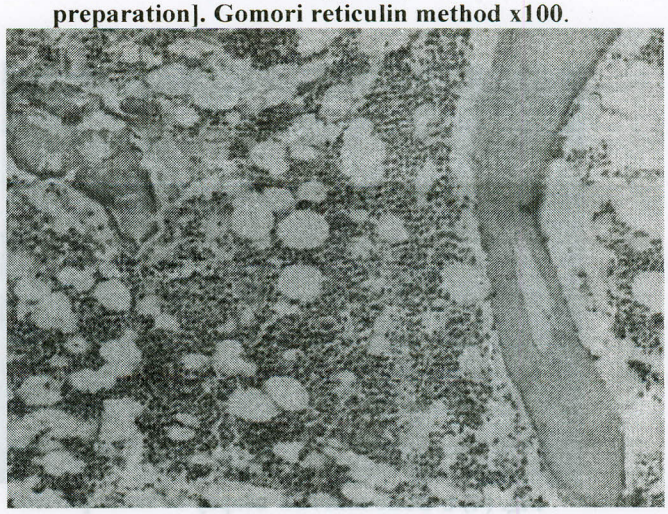

Fig (3) c.same patient during remission. H&E x 100.

Fig (3) a. interstitial pattern of bone marrow infilteration in a patient with ALL H& E x 100.

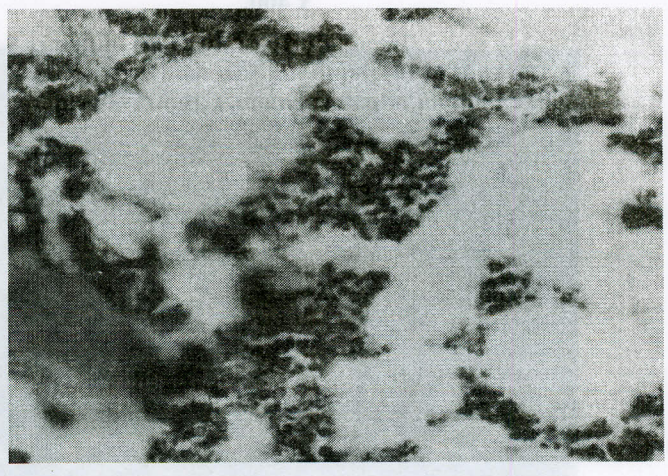

Fig (3) d.same patient during remission, reticulin decreased to normal amounts (1+). Gomori reticulin method x 100.

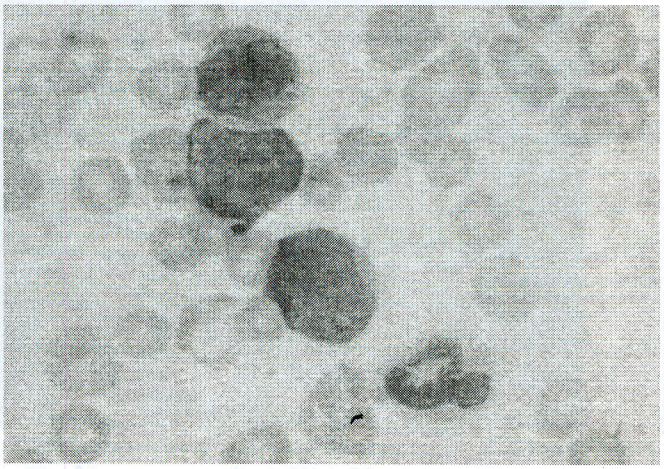

Fig (4) a. Blood film of patient with AML M_2. MGG stain x 1000.

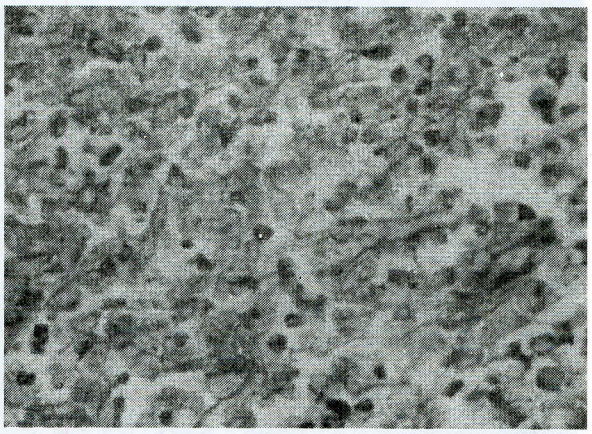

Fig. (4) b Bone marrow biopsy of same patient showing myelofibrosis (3+) diffuse, which was not apparent in the H& E stain. Gomori reticulin method x 400.

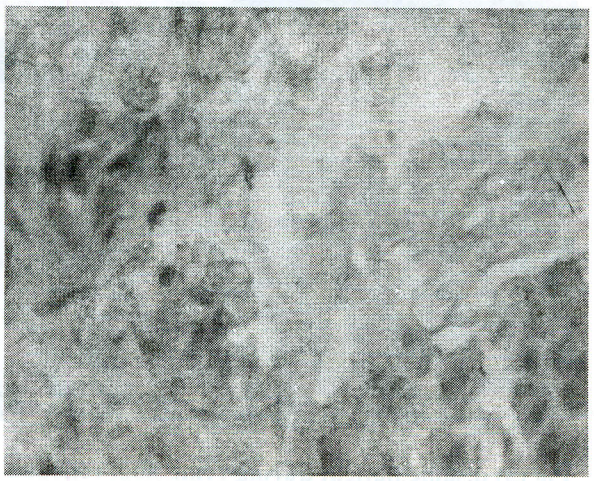

Fig. (5). Bone marrow biopsy of a patient with AML M_7 showing pericellular Fibrosis, gomori reticulin method x1000.

Discussion:

In the present study, 90% of patients with ALL & 20% of patients with AML had increased marrow reticulin at the time of initial presentation, bone marrow fibrosis was of the collagenous type in 38.9% of the patients with ALL and fibrosis, and one-third of the patients with AML with fibrosis, the fibers being of the true reticulin type (negative Van Geison stain) in the remainder of the patients in either group. The over all incidences and the incidence of collagenous type of increased reticulin were higher in this study than in previous reports [2, 5]. The frequent occurance of reticulin fibrosis was generally unsuspected in sections stained with H&E. Increased reticulin occurred in all age groups. However there was a larger number of adolescent (teenage group), in patients with ALL 50% of this group were between 13-18 years of age. Increased reticulin was often present quite early in ALL, of the total of 18 patients who had increased reticulin on admission, 13 had a history of one month or less. This finding suggests that duration of disease is only a minor factor in reticulin fibrosis . The appearance of reticulin fibrosis before the institution of chemotherapy and the similarity of treatment in all patients make it appear unlikely that chemotherapy contributes to reticulin fibrosis. Patients with ALL were found to have high incidence of myelofibrosis (90%) than those with AML (20%), this probably due to an immunological reaction which may stimulate a fibroblastic reaction and the high incidence of bone marrow necrosis in ALL [7]. Osteomylosclerosis which is a well developed finding in primary myelofibrosis could be seen in acute leukemia.

Refernces

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