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Bone Marrow Involvement and Myelofibrosis in Hodgkin's Disease

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Abstract: The importance of bone marrow biopsy in Hodgkin's disease is well known. The incidence of bone marrow involvement in Hodgkin's disease varies from 2% to 29%. The presence of myelofibrosis is not sufficent evidence for a definitive diagnosis of bone marrow involvement. Patients having myelofibrosis as a first symptom without peripheral lympadenopathy must be distinguished from patients with idiopathic myelofibrosis. In this study, we examined the frequency of bone marrow involvement and the degree of myelofibrosis in Hodgkin's disease. We found the incidence of bone marrow involvement to be 5.26%, and that of myelofibrosis to be 31.6%. The high incidence of myelofibrosis in Hodgkin's disease suggests that Hodgkin's disease must be investigated for early diagnosis and therapy in the case of idiopathic myelofibrosis.

Key Words: Hodgkin's disease, myelofibrosis.

Introduction

Fibrosis of the bone marrow accompanies many malign and non-malign diseases. When excessive fibrosis occurs, it presumably impedes heamapoesis (1). Foci of myelofibrosis in the absence of Reed Sternberg cells of mononuclear variants in Hodgkin's disease (HD) may lead to misdiagnosis, especially if peripheral adenopathy is absent (2).

Involvement of the bone marrow is an uncommon clinical presentation of HD. However, when patients with HD are examined for the presence of bone marrow involvement, it is found in 2% to 29% of previously untreated patients. Compared with patients lacking marrow involvement, these tend to be older and male , with more frequent cytopenies and symptoms of systemic disease. In general, patients with marrow involvement are reported to have short survival times, increased sensitivity to the myelosupressive effects of chemotherapy and early relapse (3).

In this study, we examined the frequency of bone marrow involvement and degree of myelofibrosis in HD.

Materials and Methods

Three hundred eleven bone marrow biopsies from January 1988 to July 1993 showing various diseases were identified from the records of the Pathology Department at Osmangazi University Medical School. All biopsies were performed with a Jamshidi needle approximately 2x0.2x0.2 cm in dimension. All of the specimens were fixed in formaline, decalcified for one day and embedded paraffin. Four-to-five µm thick sections of each bone marrow biopsy stained with hematoxylin and eosin, Gomori's silver impregnation and Trichrome Masson were reexamined.

The material was analysed using the following criteria:

Diagnosis of HD was made by lymph node biopsy. Bone marrow involvement was diagnosed when typical Reed Sternberg cells or mononuclear variants were found in a cellular environment composed of fibrous connective tissue containing lymphocytes, eosinophils, plasma cells and histiocytes, characteristic of HD.

Idiopathic myelofibrosis was defined by unexplained excessive accumulation of connective tissue in the bone marrow. Within this group, chronic megakaryocytic granulocytic myelois (CMGM) (=Agnogenic myeloid metaplasia) was defined by the presence of myelofibrosis, leuco-erytroblastic anemia, anisopoikilocytosis and a large spleen with extra medullar haematopoesis. Histological diagnosis of CMGM was made with a conspicuous

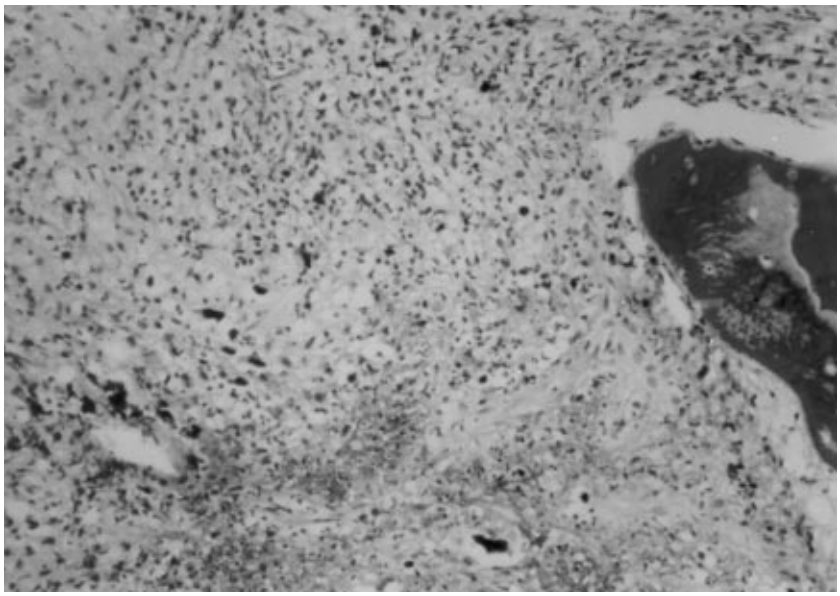

Figure 1. Bone marrow fibrosis (++++) and necrosis in a HD case. Trichrome-Masson x 200.

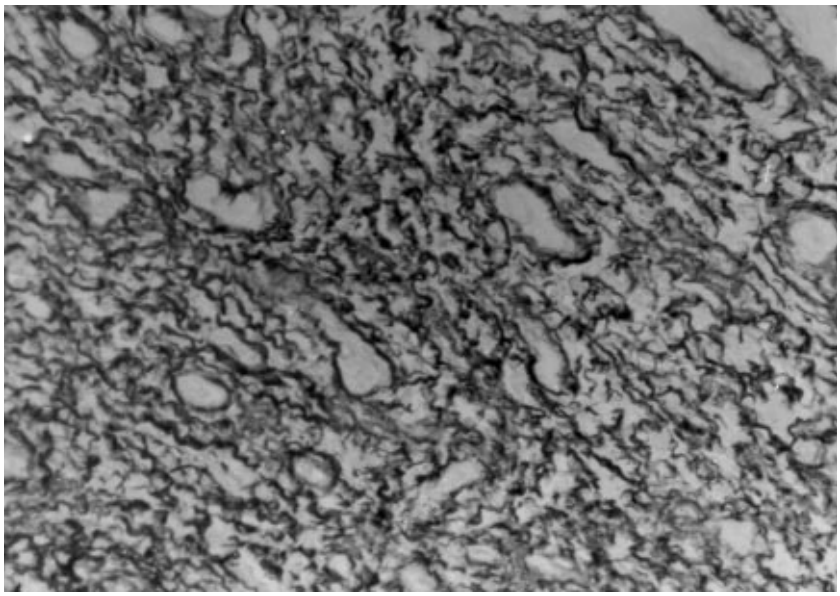

Figure 2. Reticuline fibrosis of bone marrow of the same case. Gomori's silver impregnation x 200.

proliferation of megakaryocytes having deeply lobulated nuclei of light chromatin appearance and concentrated in groups or clusters around or within sinuses.

Myelofibrosis was semiquantitatively scored: No increase in reticulin fibers (-), slight (+), moderate (++) and severe (+++). In addition, increases in collagen fibers were scored (++++).

Marrow cellularity was categorised as hypocellular, normocellular, or hypercellular.

Megakaryocyte counts in per mm^2 were calculated in all cases to differentiate CMGM from idiopathic cases.

The medical records of all patients were reviewed to provide the clinical and laboratory information to substantiate the clinical diagnosis.

Results

Of 311 patients with various diseases, 19 had HD. Myelofibrosis were assessed in 25% (78/311) of total biopsies. Myelofibrosis seen in HD patients comprised 7.7% (6/78) of all myelofibrotic cases. 8.9% (7/78) of all myelofibrotic cases were idiopathic.

There were 13 male and 6 female patients in the HD

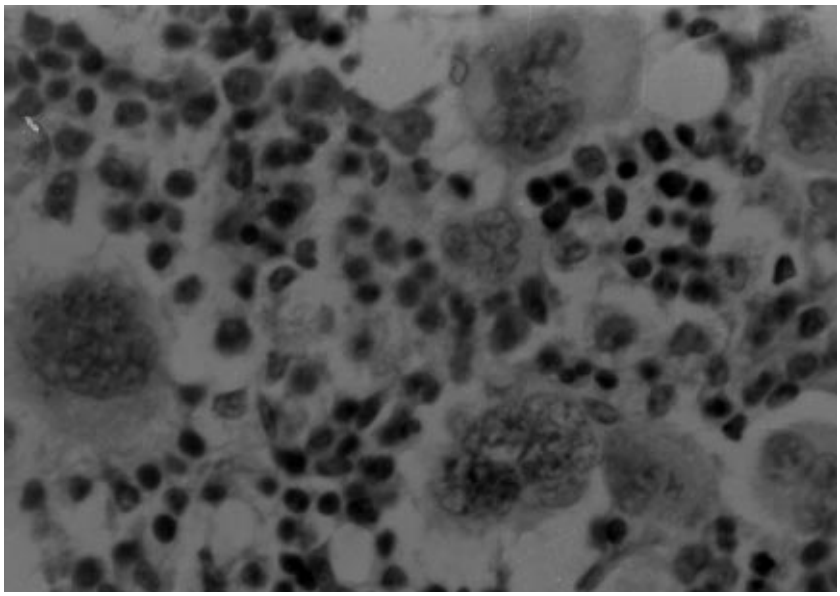

Figure 3. Megakaryocytic features of CMGM. Hematoxylin eosin x 200.

group, of ages ranging between 23 and 69 years. Through lymph node biopsy, we diagnosed nodular sclerosis in 5 cases, mixed cellularity in 9 cases, transition to lymphocyte depletion in 1 case and lymphocyte depletion in 3 cases. Lymph node biopsy of in one case, the lymph node biopsy had been performed by another laboratory, so we were unable to obtain any information regarding its histopathologic type.

Bone marrow involvement was seen in one case (5.26%). In this case, (+++) degrees of myelofibrosis were found. Myelofibrosis was determined in 31.6% (6/19) of all HD patients. Myelofibrosis was seen to be (+++) degrees in 4 cases and (++++) degrees in 2 cases (Figures 1-2).

The histopathologic subtypes of HD showing myelofibrosis were as follows: two cases of nodular sclerosis, 2 cases of mixed cellularity and 2 cases of lymphocyte depletion.

Of 19 HD patients, 7 had hypocellular, 1 had hypercellular and 8 had normocellular bone marrow. Hematopoetic cells were depressed by fibrosis in 3 cases.

In our study, 2 control biopsies were taken from 2 patients after chemotherapy, and in one case 2 biopsies were taken from each sacroiliac bone before chemotherapy.

While one of the patients had (++++) degrees of myelofibrosis before chemotherapy, the follow-up biopsy was non-fibrotic and hypocellular. The other case had hypocellular bone marrow in the first biopsy while necrosis was seen in the fibrotic ground in the control biopsy. In another case the left sacroiliac bone biopsy revealed (+++) degrees of fibrosis while the right sacroiliac bone biopsy revealed only focal fibrosis.

Megakaryocyte counts ranged from 0 to 5.90. The mean megakaryocyte count in the HD group was 1.796±0.423.

All patients between stage I and stage IIIA were treated by radiotherapy, while all other paitents received chemotherapy. The histopathologic findings, stages and survival rates are shown in Table 1.

The idiopathic myelofibrosis group consisted of 5 male and 2 female patients aged from 34 to 72 years. CMGM was diagnosed in 3 patients with increased megakaryocyte counts and features of megakaryocytes. Two patients showed transition to leukemia, at 9 and 14 months after the first bone marrow biopsies. Two patients, 60 and 72 years old, survived 2.5 and 12 months, respectively, after diagnosis of idiopathic myelofibrosis. Autopsies were not performed. Megakaryocyte counts ranged from 0.33 to 68.43 (Figure 3). Clinical and histopathological findings and survival times of the cases are shown in Table 2.

Discussion

The incidence of bone marrow involvement in HD varies from 2% to 29% in previously untreated patients. Marrow involvement is in instances the result of a widely disseminated disease; in rare cases, marrow may be involved by direct extension from involved lymph nodes. The majority of patients with bone marrow involvement

Table 1. Histopathologic findings, stages and survivals of the Hodgkin's cases.

Case	Age	Sex	Histopathologic type	Bone marrow involvement	Degrees of myeltofibrosis	Structure of Bone marrow	Stage	Survivals of cases (months)
1	28	F	NS	-	++++	Depressed	IIIB	22
2	41	M	NS	+	+++	Depressed	IVB	21
3	43	M	MC	-	+++	Normocellular	IIA	75 still living
4	32	F	MC	-	+++	Hypocellular	IIA	43
5	43	M	LD	-	++++	Depressed	IIIB	8 no examination after that date
6	58	M	LD	-	+++	Hypocellular	IIIB	9 no examination after that date
7	23	M	NS	-	-	Normocellular	IIIB	26
8	38	M	NS	-	-	Hypercellular	IB	190 still living
9	37	M	NS	-	-	Hypocellular	IIIB	17
10	60	F	MC	-	-	Normocellular	IIIB	18
11	58	M	MC	-	-	Normocellular	IIA	No examination after radiotherapy
12	48	M	MC	-	-	Normocellular	IIB	76 still living
13	48	F	MC	-	-	Hypocellular	IIIB	89 still living
14	65	M	MC	-	-	Hypocellular	IIA	17
15	69	F	MC	-	-	Normocellular	IIIB	8
16	42	F	LD	-	-	Hypocellular	IIIB	75
17	32	M	Unknown	-	-	Normocellular	IIA	74 still living
18	48	M	MC	-	-	Hypocellular	-	13
19	63	M	Transition from MC to LD	-	-	Normocellular	IIA	No examination after radiotherapy

NS: Nodular Sclerosis, MC: Mixed Cellularity, LD: Lymphocyte Depletion

Table 2. Clinical, histopathological findings and survival of idiopathic cases.

Age & Sex	Diagnosis	Degrees of Fibrosis	Megakaryocte counts	Hepatomegaly	Splenomeglay	LAP	Survival (months)
34 F	CMGM	++	68/mm^2	-	+	-	2 no examination
72 F	CMGM	++++	32/mm^2	+	+	-	3 no examination
64 M	CMGM	+++	32/mm^2	+	Splenectomy	+disseminated	72 no examination
60 M	Idiopathic	++++	3/mm^2	+	+	+micro LAP	2.5
72 M	Idiopathic	++	0.5/mm^2	+	+	-	12
63 M	Idiopathic (transition to leukemia)	+++	1.8/mm^2	+	+	-	9 no examination
37 M	Idiopathic (transition to leukemia)	++++	6/mm^2	+	+	-	14

at the time of diagnosis have mixed cellularity or cells of the nodular sclerosis type in the lymph node. Bone marrow involvement is the most unusual in the lymphocyte predominant type. The lymphocyte depletion type, an uncommon form of HD, has a high incidence (approximately 50%) of marrow involvement (3).

The quantity of the bone marrow biopsy is important for the diagnosis of bone marrow involvement, especially in myelofibrotic cases. Previous reports stressed the limitations of aspiration techniques for the diagnosis of HD in bone marrow (3, 4).

Of 19 HD cases, we determined bone marrow involvement in one case (5.26%) and various degrees of myelofibrosis in six cases (31.6%). Myelofibrosis was diagnosed histopathologically in 2 cases of nodular sclerosis, in 2 cases of mixed cellularity and in 2 cases of lymphocyte depletion.

Sabrinho-Simoes et al. (4) described the necropsy of 9 HD patients with intradiaphragmatic visceral organ involvement; only two were diagnosed antemortem with HD. Surveys of all cases lasted less than 6 months. They showed (+++) degrees of myelofibrosis in 4 cases and (+) degree of myelofibrosis in one case. Mixed cellularity was diagnosed in 2 cases and lymphocyte depletion in 7. The duration of symptoms prior to presentation ranged from 1 to 12 months. All bone marrow biopsies in this study done by aspiration, so bone marrow involvement was not seen despite widespread diseases.

Because the clinical presentation in some patients with lymphocyte depletion HD is characterised by little or no peripheral lymphadenopathy, the initial diagnostic specimen may be the bone marrow biopsy (2, 3).

Meadow et al. (2) described 4 patients with concurrent HD and bone marrow fibrosis. Their first symptom was cytopenia. These findings were associated with a delayed diagnosis for a average of 20 months.

The diagnosis of HD with marrow fibrosis must be distiguished from idiopathic myelofibrosis, especially if peripheral lymphadenopathy is absent (2).

Histopathologic examination of bone matter may reveal CMGM to differ from idiopathic myelofibrosis with megakaryocyte count and megakaryocyte morphology (5). HD may differ from CMGM by a younger age, male predominance and B symptoms (2). HD may differ from CMGM by a younger age, male predominance and B symptoms (2). CMGM is characterized by myelofibrosis, leuko-erytroblastic anemia, anisopoikilocytosis and a large spleen with extramedullar haematopoesis. Myelofibrosis has an important role in the pathogenesis of leukoerythroblastosis (5-7).

Leuko-erytroblastic anemia is indicated by immature myeloid cells and nucleated red cells in peripheral blood. It may be seen with malign and non-malign conditions such as metastatic cancer, lymphoma, some Hodgkin's cases, haemorragic infections, hypoxy and hemolysis (8).

The use of monoclonal antibodies directed against tumor antigens on the Reed Sternberg cell might be useful in differentiating marrow fibrosis due to HD from that due to idiopathic myelofibrosis (2). A combination of CD15, CD30, CD45 has been said to give reliable results in the diagnosis of HD (9).

The cause of marrow fibrosis seen in HD is unclear. Stromal damage, inflammatory infiltration and disturbed erytropoesis appear in HD caused by tumors. In the few patients with HD who have been studied, an increase in type III collagen was observed; such collagen is not a normal constituent of bone osteoid and suggests stimulation of the surrounding mesenchyme. The combination of fibroblast stimulation and myelosupression that occurs in HD suggests that a recently described growth inhibitor, tranforming growth factor beta, may be involved (2).

Meadow et al. and some other researchers have observed that marrow fibrosis resolved at least partially after chemotherapy (2). In our study, one case had an increase in myelofibrosis, while another case had a decrease in fibrosis after chemotherapy. Different degrees of fibrosis were assessed in each sacroiliac bone in the third patient. These findings were not compatible with literature.

In summary, our study and other literature indicate a high rate of myelofibrosis in HD. This findings suggested that if initial diagnostic specimens show bone marrow fibrosis without peripheral lymphadenopathy, HD must be investigated to make an early diagnose and begin therapy.

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