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Pattern of ^{111}In-chloride bone marrow scintigraphy in myelodysplastic syndrome; comparison with clinical characteristics

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^{111}In-chloride bone marrow scintigraphy (bone marrow scintigraphy) was performed in patients with myelodysplastic syndrome (MDS), tracer accumulation was classified into patterns, and the relationship between the accumulation patterns and prognostic factors was investigated to assess the usefulness of bone marrow scintigraphy.

The subjects were 14 patients diagnosed with MDS. Accumulation of the bone marrow scintigraphy tracer was classified according to the degree of accumulation in the axial bone marrow and peripheral expansion. International Prognostic Scoring System (IPSS), which are frequently used for prognostic evaluation of MDS, and conversion to leukemia were investigated in prognostic factors. We also investigated the relationship between enlargement of the liver and spleen and the prognostic factors.

The accumulation patterns were as follows: pattern I, The normal accumulation pattern (2 cases); pattern II, the expanded accumulation pattern (6 cases); pattern III, low accumulation pattern (5 cases); and pattern IV, heterogeneous accumulation pattern (1 case). The relationships between the two prognostic factors and accumulation patterns were investigated, and the prognosis was found to be significantly poorer in the patients with the low accumulation pattern than the expanded accumulation pattern. Enlargement of the liver and spleen was not significantly correlated with the prognostic factors.

Key words: ^{111}In-chloride, bone marrow scintigraphy, myelodysplastic syndrome

INTRODUCTION

INADEQUATE ERYTHROPOIESIS OCCURS in myelodysplastic syndrome (MDS), because of a qualitative abnormality in hematopoietic stem cells, and despite the cytopenia in the peripheral blood the bone marrow appears normal or hyperplastic. The incidence of MDS is higher in the aged, and the disease course is relatively long. Treatment consists of blood transfusion and cytokine therapy with erythropoietin and granulocyte colony-stimulating factor for cytopenia and induction of differentiation, but regardless of which therapy is used, the blood parameters rapidly deteriorate when it is discontinued. Bone marrow transplantation is uncommon because most of these patients are aged, and the indications have not been established. Prediction of the outcome after therapy is very important in deciding on the timing of bone marrow transplantation clinically.

The bone marrow scintigraphy tracer ^{111}In-chloride binds to serum transferrin, and the kinetics of its incorporation into protoerythrocytes is almost the same as that of iron ions. Its uptake is correlated with the activity of the erythroblast lineage and reflects the bone marrow hematopoietic nests. The bone marrow scintigraphic findings in MDS were expected to be characterized by the detection of normal or expanded hematopoietic nests, reflecting the clinical features of MDS. However, we have encountered MDS patients with various degree of bone marrow accumulation on bone marrow scintigraphy.

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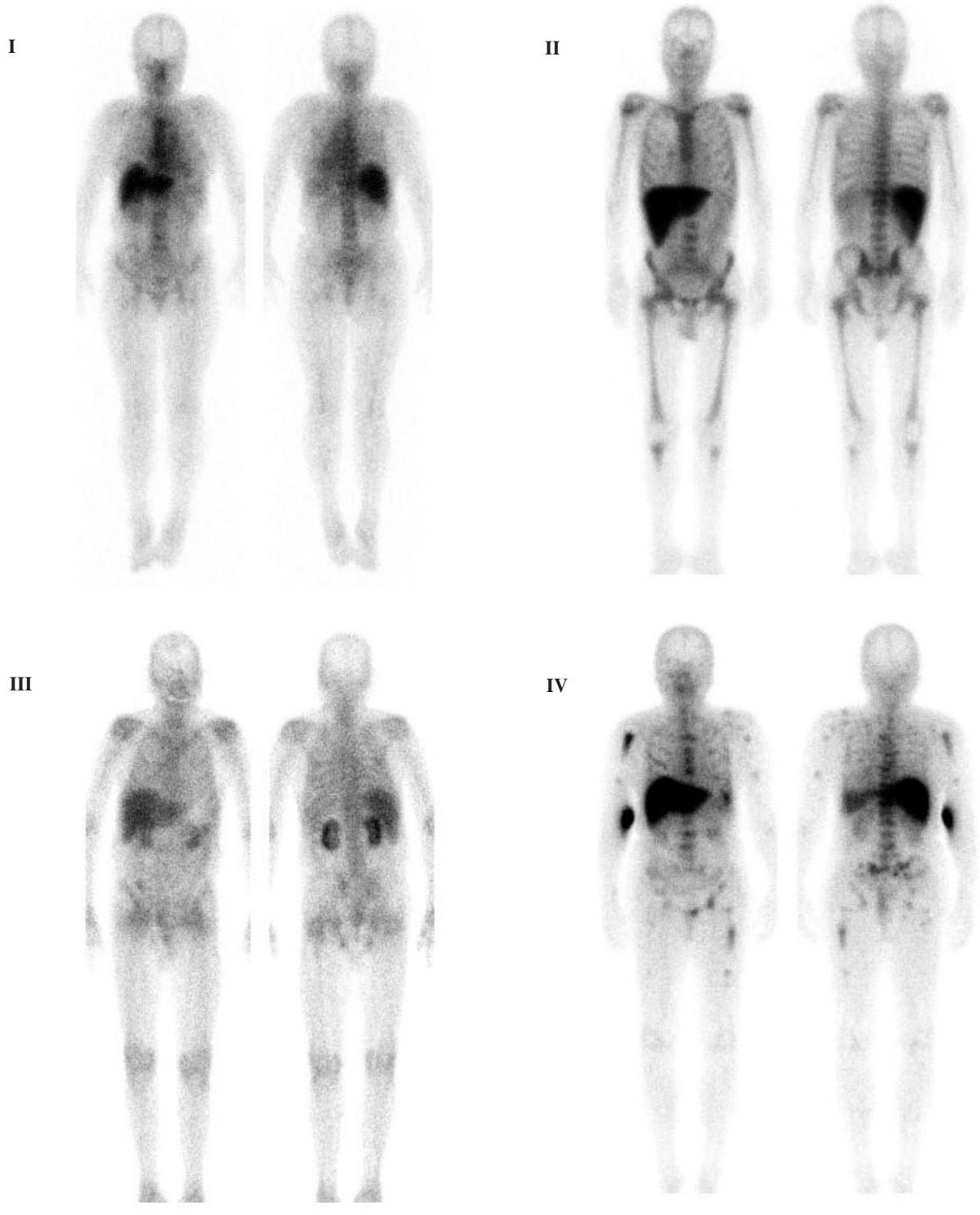


Fig. 1 Bone marrow scintigraphy accumulation patterns. I, Normal accumulation pattern; II, Expanded accumulation pattern; III, low accumulation pattern; IV, Heterogeneous pattern

Although correlations between the prognosis of aplastic anemia and the bone marrow scintigraphy findings have been investigated in many studies,[1–4] no studies on correlations in MDS have been reported, and there have been no reports focusing solely on MDS patients.

In this study we classified the tracer accumulation patterns of patients diagnosed with MDS and compared prognostic factors between patterns to investigate the

usefulness of bone marrow scintigraphy in the differential diagnosis of MDS.

MDS sometimes causes enlargement of the liver and spleen as a result of extramedullary hematogenesis, and since we detected an enlarged liver and spleen by bone marrow scintigraphy in several cases, we added enlargement of the liver and spleen to the accumulation pattern and investigated whether the prognostic factors were significantly different.

The clinical usefulness of bone marrow scintigraphy in MDS was investigated based on the results.

METHODS

The subjects were 14 patients who had been diagnosed with MDS based on the bone marrow aspiration and hematology findings and underwent ^{111}In-chloride scintigraphy at our institution between January 1995 and August 2002. There were eight males and six females, who ranged in age from 24 to 83 years (mean age; 56 years). According to the French-British-American (FAB) classification, the MDS was classified as primary refractory anemia (RA) in 4 patients, refractory anemia with excess myeloblasts (RAEB) in 6 patients, and RAEB in transformation (RAEB-t) in 4 patients. RAEB-t is classified as leukemia in the new WHO classification.

Table 1 International prognostic scoring system

Prognostic factor	score				
	0	0.5	1.0	1.5	2.0
Myeloblast ratio (%)	< 5	5–10	—	11–20	21–30
Chromosomal karyotype*	good	inter-mediate	poor		
Cytopenia	0.1	2/3			

* chromosomal karyotype
good: normal; poor: complex (less than 3 abnormalities) or chromosome 7 abnormalities; intermediate: other abnormalities; total score: low, 0; intermediate-1, 0.5–1.0; intermediate-2, 1.5–2.0; high, more than 2.5

It has been reported that accumulation of ^{111}In-chloride during scintigraphy does not reflect actual bone marrow function when free transferrin is decreased by blood transfusion, and the accumulation in the bone marrow appears to be lower in many such patients.[2,5,6] Free transferrin is hardly ever measured at the time of bone marrow scintigraphy. Blood transfusion probably most affects free transferrin, and so all patients who had received a blood transfusion within the previous seven days were excluded from this study. The interval between bone marrow aspiration and bone marrow scintigraphy was less than two weeks. The absence of conversion to leukemia was confirmed by bone marrow aspiration at the time of the diagnosis of MDS, and none of the patients were being treated at the time of the bone marrow scintigraphy. Liver enzymes were slightly elevated in only one patient, and no other patients had evidence of liver dysfunction.

The ^{111}In-chloride 111 MBq (Nihon Medi-Physics Co.) for bone marrow scintigraphy, was injected intravenously, and anterior and posterior planar views were obtained 48 hours after the injection. Images were acquired with a 2-detector-type gamma camera equipped with an intermediate-energy-type general-purpose collimator. A PRISM2000XP gamma camera (Philips Co., Cleveland, USA) was used.

Table 2 Patient characterisitics

No.	Age	Sex	Pattern	FAB classification	Enlargement of liver and spleen	IPSS score				Conversion to leukemia	Outcome
						peripheral blood	karyo-cyte	blast	total		
1	61	F	I	RA	0	0.5	0	0	0.5		—
2	83	F	I	RA	0	0.5	0	0	0.5		alive
3	65	M	II	RAEB	0	0.5	0	0.5	1.0		alive
4	24	F	II	RAEB	2	0.5	0.5	0	1.0		—
5	70	F	II	RAEB	1	0.5	0	0.5	1.0		—
6	71	F	II	RA	0	0.5	0	0.5	1.0		died
7	60	M	II	RAEB	0	0.5	0	1	1.5		—
8	58	M	II	RAEB	1	0.5	0	0.5	1.0		alive
9	42	M	III	RAEB-t	2	0.5	0	0.5	1.0	9 months	died
10	68	M	III	RAEB-t	0	0.5	1.0	1.5	3.0	4 months	died
11	37	F	III	RAEB	0	0.5	0	1.5	2.0	6 months	died
12	72	M	III	RAEB-t	0	0.5	0.5	2	3.0	22 months	alive
13	52	M	III	RAEB-t	0	0.5	1.0	2.0	3.5		died
14	81	M	IV	RA	0	0.5	0	0.5	1.0		—

Patient number, Age, Sex, Accumulation pattern, FAB classification, Enlargement of the liver and spleen, IPSS severity score, Conversion to leukemia (after diagnosis by aspiration biopsy), Outcome of in patients with myelodysplastic syndrome (follow-up period: was 60 months)

The accumulation in the vertebrae, sternum, pelvis, cranial bones, scapula, and proximal 1/3 of the femur and humerus observed by bone marrow scintigraphy in normal adults was designated "axial bone marrow," and accumulation in the peripheral femur, distal humerus, and forearm bones was designated "peripheral expansion." The axial bone marrow and peripheral expansion accumulations were classified into the following four patterns (Fig. 1):

I. Normal accumulation pattern
II. Expanded accumulation pattern: Normal-high accumulation in axial bone marrow plus peripheral expansion
III: Low accumulation pattern: Low accumulation in axial bone marrow and no peripheral expansion
IV: Heterogeneous accumulation pattern: Heterogeneous accumulation in axial bone marrow plus peripheral accumulation

Enlargement of the liver and spleen was scored as follows:

0: both liver and spleen are of normal size.
1: either the liver or spleen is enlarged.
2: both the liver and spleen are enlarged.

Two radiologists certified for nuclear medicine jointly made the judgments on bone marrow scintigraphy accumulation.

Evaluation of the prognosis: Since some patients could not be clinically evaluated for prognosis, prognostic score and conversion to leukemia were used as indices reflecting the prognosis. Prognosis was scored according to the International Prognostic Scoring System (IPSS) (Table 1), with higher scores indicating a poor prognosis. The scores are useful for predicting outcome,[7] and are widely used for MDS. Prognosis in this study was scored according to the IPSS diagnostic criteria and investigated for correlations with the accumulation patterns.

The clinical course and outcome between 1995 and 2000 were followed, and the characteristics of the accumulation patterns were investigated in patients diagnosed with conversion to leukemia based on bone marrow aspiration and blood findings.

Correlations between accumulation patterns and two parameters, prognostic score and conversion to leukemia, were analyzed by the Kruskal-Wallis test, and $p < 0.05$ was regarded as significant.

RESULTS (Table 2)

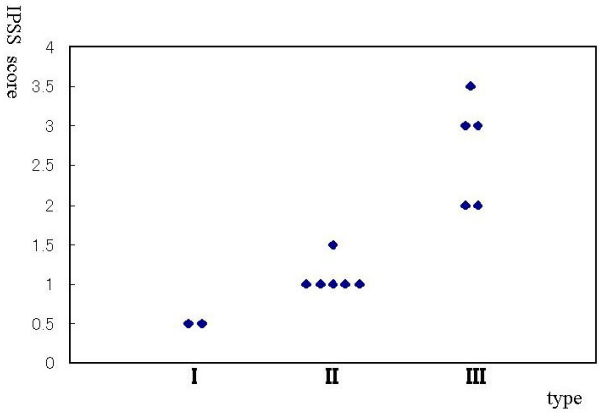
1) Numbers of patients according to accumulation pattern

The accumulation pattern was type I in 2 cases, type II in 6 cases, type III in 5 cases, type IV in 1 case.

2) Relationship between accumulation pattern and IPSS score

A significant correlation was observed between the accumulation patterns and prognostic score ($p < 0.01$). The scores of the patients with the normal accumulation type were lowest (Table 2). Prognostic score was higher in the patients with the low accumulation type than in those with the expanded type. Of the three parameters of the IPSS score, peripheral blood cytopenia, chromosomal aberration, and myeloblast count, only the myeloblast count was correlated with the accumulation patterns. No significant correlations were found with peripheral blood cytopenia ($p < 0.75$) or chromosomal aberrations ($p < 0.43$).

Table 3 Correlation between accumulation patterns (I, II, III type) and IPSS prognostic scores



3) Relationship between accumulation patterns and conversion to leukemia

There was a significant correlation between the accumulation patterns and conversion to leukemia ($p < 0.02$). Conversion to leukemia occurred in four of the 14 patients, all of whom had the low accumulation type.

4) Relationship between accumulation patterns and prognostic score

Five of the 14 patients could not be followed up. Of the remaining nine patients, four were alive while five died after a mean follow-up period of sixty months. One of the five patients who died had the expanded type and the other 4 had the low accumulation type. The survival time of the patient with the expanded accumulation type who died was seven months, and the mean survival period of the 4 patients with the low accumulation type was 10.1 months. The cause of death of the patient with the expanded accumulation type was unrelated to MDS, whereas the causes of the deaths of the four patients i.e., conversion to leukemia, and sepsis and multiple organ failure after transplantation of peripheral blood stem cells with the low accumulation type, were attributable to MDS.

5) Relationship between liver and spleen enlargement and the IPSS scores and conversion to leukemia

Enlargement of the liver and spleen was not significantly

correlated with the IPSS scores ($p < 0.69$) or conversion to leukemia ($p < 0.69$).

6) The patient with the heterogeneous accumulation type had stomach cancer as a co-worbidity. MRI and bone scintigraphy performed at almost the same time confirmed the presence of multiple bone metastases and many of the regions of accumulation on the bone scintigram were absent on the bone marrow scintigram.

DISCUSSION

The bone marrow in MDS is generally normal to hyperplastic, but cytopenia occurs in peripheral blood, with abnormal morphology in each blood cell lineage, and the disease progresses chronically for several months to several years. The incidence of MDS is higher in the middle-aged and aged, and MDS is characterized by the development of leukemia in a high proportion of patients. The prognosis of MDS is governed by infection and hemorrhage, resulting in death by bone marrow failure or conversion to leukemia. Although no reliable therapy is currently available, treatments can be roughly divided into blood transfusion, with the aim of improving the cytopenia, blood cell differentiation induction therapy with Ara-C, antitumor chemotherapy, and bone marrow transplantation. However, powerful chemotherapy such as used to treat acute leukemia is avoided, because many MDS patients are aged, and recovery of normal stem cells from chemotherapy-induced inhibition of the bone marrow is likely to be delayed, leading to a higher risk of death from infection. Although in recent years bone marrow transplantation has become potentially curative, the criteria for the timing of transplantation have not been established.

^{111}In-chloride bone marrow scintigraphy is used as a method of imaging bone marrow function, and its application to aplastic anemia,[1–5,8–11] myelofibrosis,[5,9,12] leukemia,[2] malignant lymphoma,[13] and bone marrow metastasis of gastric cancer[14] has been assessed, but there have been no reports on MDS patients alone. Although the correlation between the outcome of aplastic anemia and bone marrow scintigraphy findings have been investigated in many studies,[2–4] there have been no reports focusing on the correlations in MDS.

In this study we investigated the accumulation patterns and prognosis of MDS, with abnormal accumulation roughly classified into an expanded type and low accumulation type. The normal accumulation type had the best prognosis. The prognosis was better and the risk of conversion to leukemia was lower in the patients with the expanded accumulation type with peripheral expansion than in those with the low accumulation type without peripheral expansion. These findings contradicted studies that found that in patients with aplastic anemia, leukemia, bone metastasis, and malignant lymphoma, peripheral expansion responded poorly to therapy and was a portent of poor prognosis.[2,4] We assumed that the bone marrow is normal or hyperplastic in the early stage of MDS, and that the presence of peripheral expansion when hypoplasia progresses or conversion to leukemia occurs indicates that the compensatory function of the bone marrow remains intact.

All patients whose MDS converted to leukemia exhibited the low accumulation pattern, suggesting that the bone marrow scintigraphic features at the time of conversion to leukemia are an absence of peripheral expansion and slow decrease in accumulation in axial bone marrow. Since all patients who developed bone marrow failure attributable to MDS and all of those who died after conversion to leukemia exhibited the low accumulation pattern, it may be beneficial to perform bone marrow transplantation in patients with the low accumulation pattern in view of this risk.

Some patients (Nos. 3, 8, 9 Table 2) had different type in bone marrow scintigraphy despite having the same IPSS score, and the bone marrow scintigraphy patterns reflected the prognosis better in some cases than the IPSS score.

The only IPSS prognostic classification parameter that was correlated with the accumulation patterns was the myeloblastic count, which was higher in the patients with the low accumulation type. This finding was similar to the findings in previous reports on aplastic anemia,[9] suggesting that the accumulation of ^{111}In-chloride corresponded to the degree of bone marrow cellularity.

Hematopoiesis in yellow bone marrow, liver, and spleen is also used as an index of compensatory function for hematopoietic nests. Enlargement of the liver and spleen was observed in some patients in this study, but no correlations with severity or conversion to leukemia were found, in contrast to peripheral expansion. Since enlargement of the liver and spleen is not directly related to hematopoiesis in the liver and spleen, it may be better to use accumulation in bone marrow (axial accumulation and peripheral expansion) as an index of the compensatory function of hematopoietic nests.

One patient exhibited island-like heterogeneous accumulation, but the patient had concurrent bone metastase of stomach cancer, and bone marrow accumulation was low in the multiple bone metastasis regions. MDS frequently occurs in aged people, and since some patients may have multiple co-morbidities accompanied by bone lesions, additional bone scintigraphy and investigation of the medical history may be necessary.

In conclusion, the tracer accumulation pattern obtained by bone marrow scintigraphy and the relationships between the prognosis and each of the patterns were investigated in MDS patients. The outcome of MDS can be predicted from the bone marrow scintigraphy accumulation pattern, suggesting its clinical usefulness.

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