

Incidence and Characteristics of Lymphoid Malignancies in Untreated Myelodysplastic Syndromes

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We have analyzed 1,198 patients with untreated myelodysplastic syndromes (MDS) with two main objectives: (1) to determine the prevalence of lymphoid malignancies (LM) in MDS patients; and (2) to ascertain whether there is some relationship between the MDS subtype and the LM type. In fourteen of 1,198 primary MDS patients (1%) (4 with refractory anemia, 3 with refractory anemia with ring sideroblasts, 2 with refractory anemia with excess of blasts and 5 with chronic myelomonocytic leukemia) a LM was detected. In all cases, the LM was of the B-cell type: 6 cases of chronic lymphocytic leukemia, 5 cases of lymphoplasmacytoid lymphoma, and 3 cases of multiple myeloma. B-cell malignancy did not prevail in any MDS subtype and no correlation was observed between the different varieties of both diseases. In conclusion, in this large series, 1% of the untreated patients with MDS had B-cell malignancy, an association that in most cases is likely to be merely coincidental.

KEY WORDS: myelodysplastic syndromes lymphoid malignancies

INTRODUCTION

The development of myeloid neoplasias in patients with lymphoid malignancies (LM) is a well-known fact^{1,2} which is usually attributed to the leukemogenic effect of chemoradiotherapy.^{3,4} However, there are several reports of patients in whom myelodysplastic syndromes (MDS) and LM occurred simultaneously without prior chemo and/or radiotherapy.^{2,5,6} In these reports, however, the incidence of this association has not been established.

The aims of this study were to determine the prevalence of LM in a large series of patients with primary MDS and to ascertain whether there is any relationship between the MDS subtype and the LM type.

MATERIAL AND METHODS

We retrospectively analyzed 1,198 patients with primary MDS diagnosed between 1986 and 1995 at five different institutions. Patients with prior history of chemotherapy and/or radiotherapy (secondary MDS) were not considered. MDS was diagnosed and classified on the basis of FAB criteria.⁷ The diagnosis of chronic lymphocytic leukemia (CLL) was made according to the criteria recommended by the International Workshop on CLL.⁸ SWOG criteria⁹ and the REAL classification¹⁰ were used for the diagnosis of multiple myeloma (MM) and lymphoid neoplasms, respectively. A review of peripheral blood smears, as well as bone marrow aspirates, was performed on all patients who presented the association of MDS and LM in order to analyze myelodysplastic features and lymphoid cells morphology. In 5 of 6 CLL and in all 5 lymphoplasmacytoid associated to MDS, the B nature of the neoplastic cells was confirmed by cell-surface marker analysis.

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RESULTS

Fourteen of 1,198 MDS (1%) presented a B-cell malignancy. The main clinical and biological characteristics of these patients are summarized in Table 1. There were 9 males and 5 females. The median age was 73.6 years (range: 59–86). In 12 of these fourteen cases the B-cell malignancy and myelodysplastic syndrome were diagnosed simultaneously and beforehand in the remaining two (3 and 11 years, respectively). Patient number 2 (considered as having MDS and CLL simultaneously) deserves some comment. At diagnosis some lymphoid aggregates were observed in the bone marrow biopsy in addition to some MDS features. Twenty-six months later, despite steroid therapy, this patient presented a peripheral blood picture typical of CLL. Retrospective studies, using monoclonal antibodies, proved the B-cell nature of the lymphoid aggregates at the time of MDS diagnosis.¹¹ According to the FAB criteria, patients in whom a lymphoid malignancy was also present, were classified as: 4 refractory anemia (RA), 3 refractory anemia with ring sideroblasts (RAS), 2 refractory anemia with excess of blasts (RAEB) and 5 chronic myelomonocytic leukemia (CMML). In all cases, the lymphoid malignancy was of the B-cell type: 6 cases of chronic lymphocytic leukemia (CLL), 5 cases of lymphoplasmacytoid lymphoma (LPL), and 3 cases with multiple myeloma (MM).

The three patients with MM had a monoclonal IgG K band in their serum. MM occurred simultaneously with RA, RAS and CMML. Six patients presented CLL, five of whom had a classical B-CLL immunophenotype (SmIg+ weakly positive, CD5+, CD19+, CD23+, with

light chain restriction). One patient presented a typical picture of B-CLL by morphological and cytochemical features but the immunophenotype could not be assessed.¹² Five patients had LPL with the following immunophenotype: cmIg+, CD5–/+, CD19+, CD23– and CD38+/-, coinciding with MDS at the time of diagnosis. B-cell malignancies did not prevail in any MDS subtype. Thus, 4 RA coexisted with 2 CLL, 1 LPL, 1 MM; 3 RAS with 1 CLL, 1 LPL, 1 MM; 2 RAEB with 1 CLL and 1 LPL, and 5 CMML with 2 CLL, 2 LPL, and 1 MM (Table 1).

DISCUSSION

The association between MDS and B-cell malignancy unrelated to therapy is rare.^{1–6,12–16} This is confirmed in the present report in which only 14 of 1,198 primary MDS (1%) cases presented B-cell malignancy. This association, therefore, is likely to be coincidental. In our experience, B-cell malignancy did not prevail in any particular MDS subtype and no correlation was observed between the different varieties of both diseases.

A small proportion of patients with plasma cell dyscrasias with concurrent MDS have been previously reported.^{5,13} In most cases, the MDS was secondary to myeloma therapy and most of these patients had received treatment with alkylating agents. However, in 3 reports^{2,5,14} describing a total of 11 patients, the diagnosis of MDS and MM was made simultaneously, as in our three cases. On the other hand the coexistence of MDS and CLL in untreated patients seems to be rare. Among

Table 1 Characteristics of patients with coexistence of myelodysplastic syndromes (MDS) and lymphoid malignancies (LM)

Patient	Age/Sex years	Hb g/L	WBC $\times 10^9/L$	Platelets $\times 10^9/L$	MDS Subtype	Lymphoid Disorder	Interval Between MDS&LM
1	59/M	98	16	98	RA	CLL	11 years
2	60/F	66	4.1	92	RA	CLL	Coincident
3	86/M	83	9.9	210	RA	LPL	Coincident
4	81/M	97	98	200	RA	MM	Coincident
5	73/M	114	31	276	RAS	CLL	Coincident
6	78/M	112	9.4	243	RAS	LPL	Coincident
7	79/F	90	58	298	RAS	MM	Coincident
8	78/M	58	29	12	RAEB	CLL	Coincident
9	68/F	99	6.5	141	RAEB	LPL	Coincident
10	67/M	99	68	36	CMML	CLL	Coincident
11	69/M	170	5	75	CMML	CLL	3 years
12	80/M	118	10.7	64	CMML	LPL	Coincident
13	73/F	105	13.8	273	CMML	LPL	Coincident
14	73/F	105	30	130	CMML	MM	Coincident

Abbreviations: LM, lymphoid malignancies; MDS, myelodysplastic syndromes; RA, refractory anemia; RAS, refractory anemia with ring sideroblasts; RAEB, refractory anemia with excess of blasts; CMML, chronic myelomonocytic leukemia; CLL, chronic lymphocytic leukemia; LPL, lymphoplasmacytoid lymphoma; MM, multiple myeloma.

190 patients with MDS Copplestone *et al.*⁵ found 20 cases coexistent with lymphoid malignancy; most were lymphomas or MM with CLL being observed in only 3 untreated patients (1.5%). In our experience 6 of 1,198 MDS patients had CLL, representing an even lower percentage (0.5%). The second malignancy may appear long after the diagnosis of MDS and Bastion *et al.*¹⁵ reported a patient in whom the diagnosis of MDS was followed by the appearance of CLL 9 years later. Likewise, eleven years elapsed between the diagnosis of MDS and that of CLL.

Patient no. 2, as previously mentioned in the results, is similar to another case previously reported by Tambone *et al.*¹⁶ In our case the initial study of the bone marrow histology showed some lymphoid aggregates and a number of MDS features (hypossegmentation and clumping of chromatin in neutrophils, as well as dysmorphic platelets). Twenty-six months later she presented a peripheral blood picture typical of B-CLL both morphologically and immunophenotypically. Retrospective studies proved the B nature of the lymphoid aggregates at the time of diagnosis of the MDS.

In this regard, it is worth mentioning that bone marrow lymphoid aggregates are a relatively frequent finding in the bone marrows of elderly patients and that immunological abnormalities such as a polyclonal increase of bone marrow lymphocytes are not infrequent in MDS.¹⁷ On the other hand, in a study of 68 MDS patients, five (7%) showed a B-cell population with a rearranged monoclonal immunoglobulin heavy chain gene hypervariable CDR3 region, leading to the suggestion that while some MDS may develop from a committed myeloid progenitor, those with monoclonal lymphocytes may arise from a pluripotential progenitor.¹⁸ The monoclonal origin of some of the cases might, in part, explain the coexistence of B-cell and myeloproliferative disorders and, perhaps, the more aggressive clinical course of the MDS.

The coexistence of MDS and non-Hodgkin's lymphoma is also rare.⁵ Most are of low grade B-cell type, as in our series in which 5 MDS cases were associated with a LPL.

In conclusion, in patients with untreated MDS the coexistence of MDS with B-cell malignancies appears to be extremely rare (1% in our series of 1,198 MDS patients). Although there are data indicating that immunological disturbances, including the presence of increased polyclonal and even monoclonal B-lymphocytes in the bone marrow, may be present in some patients with MDS, in other studies the concomitant existence of two different clones, separately accounting for the MDS and the B-cell malignancy, has also been

demonstrated.^{19,20} Therefore, in most instances the association of MDS with B-cell malignancies is more likely to be coincidental. However, MDS patients with an increased proportion of lymphoid cells or lymphoid aggregates in the bone marrow should be carefully studied and monitored in order to discard, or to promptly detect, an associated B-cell malignancy.

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