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Autoimmune manifestations associated with myelodysplastic syndrome predict a poor prognosis

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Abstract

We evaluated the clinical characteristics of autoimmune manifestations (AIMs) associated with myelodysplastic syndrome (MDS) to elucidate whether AIMs impacted MDS outcomes in Japan.

This retrospective study including 61 patients who received a new diagnosis of MDS between January 2008 and December 2015 was conducted by the review of electronic medical records for the presence of AIMs within a 1-year period prior to or following the diagnosis of MDS.

AIMs were identified in 12 of the 61 (20.0%) patients with MDS. The neutrophil counts and C-reactive protein levels in peripheral blood were significantly elevated in patients with AIMs, and the survival was shorter in those with AIMs compared to those without AIMs. Multivariate analysis demonstrated that the presence of AIMs and higher-risk disease according to the International Prognositic Scoring System (IPSS) were independent risk factors for increased mortality (hazard ratio, 4.76 and 4.79, respectively).

This retrospective study revealed that the prognosis was poor in patients with MDS-associated AIMs. The treatment of MDS using the current algorithms is based on prognostic scoring systems such as IPSS. Treatment strategies for patients with MDS-associated AIMs should be reconsidered, even in those with low-risk MDS according to the IPSS.

Abbreviations: AIMs = autoimmune manifestations, AML = acute myeloid leukemia, CIs = confidence intervals, CR = complete response, CRP = C-reactive protein, GVHD = graft-versus-host disease, HRs = hazard ratios, HSCT = hematopoietoic stem cell transplation, IPSS = International Prognositic Scoring System, MDS = myelodysplastic syndrome, OS = overall survival, PR = partial response, TNF-α = tumor necrosis factor α, WHO = World Health Organization.

Keywords: autoimmune disease, autoimmune symptoms, myelodysplastic syndrome, prognosis

1. Introduction

Myelodysplasic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by cytopenia, abnormal cellular morphology, and ineffective hematopoiesis. Approximately 10% to 25% of patients with MDS develop autoimmune manifestations (AIMs), including vasculitis, arthritis, thyroiditis, cutaneous lesions, interstitial pulmonary fibrosis, and neutrophilic diseases.[1,2] The AIMs can range from limited clinical symptoms to systemic diseases with vital organ damages.[3] The cause of the various AIMs that accompany MDS remains unclear. In one of the first systematic evaluations of AIMs in patients with MDS, Enright et al found that 14% of the 221 retrospectively analyzed patients had AIMs.[4] Since this first report, more than 10 retrospective studies have been conducted.[5–14] Mekinian et al compared 123 patients with MDS and reported that those with AIMs tended to be younger ($P < .01$), male ($P = .03$), and to have high-risk features such as poor karyotype and high-risk MDS according to the International Prognositic Scoring System (IPSS).[13] The authors also reported that the AIMs preceded the diagnosis of MDS in 37% of the cases and occurred concomitantly in 31% of the cases. In the remaining cases (32%), the AIMs developed after the MDS diagnosis with a median time of 8.6 months.[13]

It remains controversial whether the AIMs affect the outcome of patients with MDS. Enright et al reported that the prognosis was worse in patients with AIMs than in those without AIMs,[4]

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whereas more recent studies failed to demonstrate the adverse impact of AIMs on patients outcomes.[7,8,10] Cytogenetic abnormalities are one of the key features of MDS with prognostic significance. Lee et al reported that 5q deletion in patients with MDS was associated with neutrophilic dermatosis, which was an independent risk factor of mortality.[15]

Despite many studies on the MDS-associated AIMs, the clinical characteristics of Japanese patients exhibiting the AIMs and their potential impact on outcomes have not been reported to date. The current study aimed to address these gaps in knowledge.

2. Materials and methods

2.1. Patients

Patients who were diagnosed with MDS at the Department of Hematology, Oncology and Cardiovascular Medicine in Kyushu University Hospital between January 2008 and December 2015 were included in this retrospective study. The MDS diagnosis was based on the 2008 World Health Organization (WHO) classification.[16] To minimize selection bias, all consecutive patients during the study period were included in the study. This study was approved by the ethics committee of the Kyushu University Hospital (approval number 29-267), and the principles of the Helsinki Declaration were followed throughout the study. Because this was retrospective research, we disclosed the study information at the site of the related facilities. Obtaining patient consent was not required according to the committee's procedures.

2.2. Clinical and laboratory assessments

The following data collected at the time of MDS diagnosis were included: age, sex, MDS type according to the WHO classification, percentage of bone marrow blasts, karyotype, and other laboratory data including white blood cell and platelet counts and the levels of hemoglobin, lactate dehydrogenase, and C-reactive protein (CRP) levels. All patients were classified according to IPSS, and low and intermediate-1 risk groups were defined as the lower-risk group (IPSS < 1.5) and intermediate-2 and high-risk groups were combined as the higher-risk group (IPSS ≥ 1.5).[17]

2.3. Clinical assessment of the AIMs

The electronic medical records were systemically reviewed, and autoimmune diseases and autoimmune symptoms associated with autoimmune diseases were recorded as AIMs. Patients diagnosed by rheumatologists as having an autoimmune disease were classified in the autoimmune disease group. Autoimmune diseases searched within electronic medical records include hypothyroidism, rheumatoid arthritis, systemic vasculitis, polymyalgia rheumatica, remitting seronegative symmetrical synovitis with pitting edema syndrome, systemic lupus erythematosus, Sjogren's syndrome, myositis, systemic sclerosis, psoriasis, Behcet's disease, and Sweets's syndrome, which were determined based on previous reports.[1–3,13] Patients who had symptoms related to autoimmune diseases but were not diagnosed with an autoimmune disease were classified in the autoimmune symptom group. Autoimmune symptoms searched within electronic medical records were determined based on previous reports as follows.[1–3,13] Systemic symptom includes noninfectious fever. Mucocutaneous symptoms include aphthous stomatitis, skin lesion, and Raynaud's phenomenon. Musculoskeletal symptom includes arthritis. Respiratory symptom includes interstitial pneumonitis. Gastrointestinal symptom includes intestinal ulcer. Neurological symptom includes peripheral neuropathy. AIMs that developed more than 1 year prior to the MDS diagnosis were excluded from the analyses.

2.4. Statistical analysis

Comparisons of means and proportions between 2 groups were performed using Student's t test and Fisher's exact test, respectively. The Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the associations between MDS characteristics and mortality. The Kaplan–Meier method was used to estimate survival curves, and the log-rank test was used for comparisons. All P values were two-sided, and P values $< .05$ were considered statistically significant. All statistical analyses were performed using statistical software Stata version 14.0 (Stata Corporation, College Station, TX).

3. Results

3.1. AIMs identified in patients with MDS and the interval between the MDS diagnosis and AIM onset

A total of 61 patients were diagnosed with MDS during the study period. AIMs associated with MDS were identified in 12 of the 61 patients (20.0%). Autoimmune diseases that developed in 3 patients were intestinal Behcet's disease, systemic sclerosis, and psoriasis vulgaris in 1 patient each (Fig. 1A). Apart from them, 12 autoimmune symptoms were found in 9 patients including interstitial pneumonitis, aphthous stomatitis, small intestinal ulcer, panniculitis of lower extremities, pyoderma gangrenosum, arthritis, and noninfectious fever in 4, 3, 1, 1, 1, 1, and 1 patient, respectively (Fig. 1A). In 6 of the 12 patients (50%), the AIMs developed within 1 month before or after the MDS diagnosis. The AIMs preceded the MDS diagnosis in 3 patients (25%), whereas the MDS diagnosis preceded the AIMs in 3 patients (25%) (Fig. 1B).

3.2. Comparison of the demographic and clinical characteristics between the patients with and without the MDS-associated AIMs

We first compared the clinical characteristics of patients with and without the AIMs at the time of MDS diagnosis (Table 1). There were no differences in terms of age, sex, MDS type according to the WHO classification, and IPSS risk group. The total white blood cell, neutrophil, platelet counts, and the CRP levels in the peripheral blood were significantly elevated in patients with the AIMs as compared to those without the AIMs. These data suggested that chronic inflammation might latently exist in patients with AIMs at the diagnosis of MDS. Karyotype abnormalities were more frequent in patients with the AIMs than in those without the AIMs (91.7% vs 51.0%; $P = .02$). Trisomy 8 was found in 3 of the 12 patients with the AIMs. Among these patients, 1 developed intestinal Behcet's disease, 1 patient developed interstitial pneumonitis followed by pyoderma gangrenosum, and 1 patient presented with aphthous stomatitis and small intestinal ulcer. These results suggested that trisomy 8

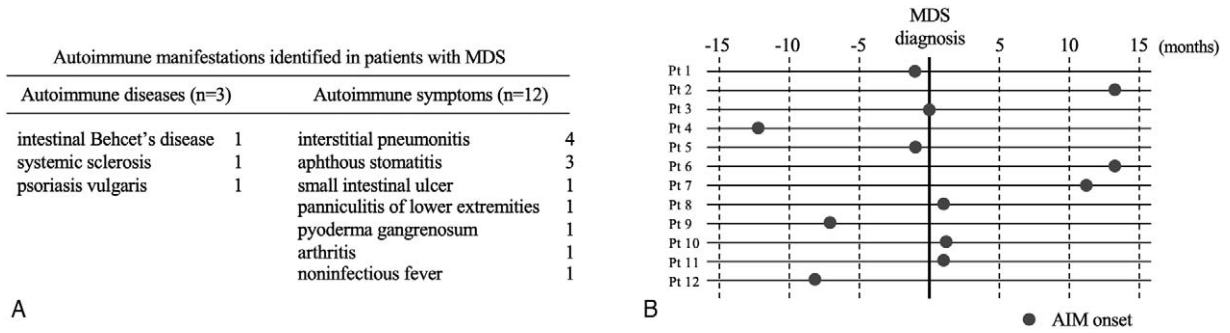

Figure 1. (A) Distribution of AIMs in patients with MDS and (B) time from MDS diagnosis to AIM onset in each patient.

was associated with Behcet's disease or Behcet's-like symptoms as previously reported.[18]

3.3. Treatments for MDS and the AIMs

The treatments for MDS were shown in Table 2. About half of all patients (66.7% in the patients with the AIMs and 46.9% in the patients without the AIMs) did not receive any treatment for MDS. Among patients treated for MDS, there were no differences in the treatments received between patients with and without the AIMs. There were 2 cases of progression to acute myeloid leukemia (AML) in patients without the AIMs, but none in the patients with the AIMs. Of the 2 patients who progressed to AML, 1 received chemotherapy and 1 was untreated and died.

With regard to the treatments for the AIMs, 6 of 12 patients were treated. The treatments included prednisolone, methylprednisolone pulse therapy, anti-rheumatic drug, topical steroid, colchicine, and biologics in 4, 2, 2, 1, 1, and 1 patient, respectively. By these treatments, initial favorable responses, as determined by the physicians, were obtained in 5 of 6 patients.

3.4. Overall survival in patients with and without the MDS-associated AIMs

Next, we compared the survival of patients with and without the MDS-associated AIMs (Fig. 2), which revealed that the overall survival (OS) was shorter in those with the AIMs than in those without the AIMs ($P = .03$ by the log-rank test). The 5-year OS rates were 44.2% and 74.6% than those with and without AIMs, respectively. In patients with the AIMs, the causes of deaths were interstitial pneumonitis, MDS, graft-versus-host disease (GVHD), and congestive heart failure in 2, 1, 1, and 1 patient, respectively. In patients without the AIMs, the causes of deaths were MDS, pneumonia, AML, GVHD, cutaneous infection, and

Table 1

Demographic and clinical characteristics of the patients with and without the AIMs associated with MDS.

	All patients (n = 61)	MDS with AIMs (n = 12)	MDS without AIMs (n = 49)	P*
Age (yr), mean (95%CI)	62.5 (58.9–66.0)	62.9 (52.3–73.6)	62.4 (58.6–66.2)	.91
Gender (female), n (%)	18 (29.5)	3 (25.0)	15 (30.6)	1.00
WHO 2008 classification of MDS				
RCUD, n (%)	17 (27.9)	3 (25.0)	14 (28.6)	.46
RARS, n (%)	2 (3.3)	0 (0)	2 (4.1)	
RCMD, n (%)	27 (44.3)	4 (33.3)	23 (46.9)	
RAEB-1, n (%)	10 (16.4)	2 (16.7)	8 (16.3)	
RAEB-2, n (%)	4 (6.6)	1 (8.3)	3 (6.1)	
MDS-U, n (%)	1 (1.6)	1 (8.3)	0 (0)	
Karyotype abnormality, n (%)	36 (59.0)	11 (91.7)	25 (51.0)	.02
Bone marrow blasts (%), mean (95%CI)	3.0 (2.1–3.9)	3.6 (0.9–6.3)	2.8 (1.9–3.8)	.50
WBC ($\times 10^9$/L), mean (95%CI)	3.9 (3.1–4.6)	6.4 (3.0–9.7)	3.3 (2.8–3.8)	<.01
Neutrophil ($\times 10^9$/L), mean (95%CI)	2.2 (1.7–2.7)	4.1 (2.2–6.1)	1.8 (1.4–2.1)	<.01
Lymphocyte (x10^9/L), mean (95%CI)	1.1 (0.9–1.2)	1.0 (0.6–1.4)	1.1 (0.9–1.3)	.63
Hb (g/dL), mean (95%CI)	9.4 (8.9–10.0)	9.2 (8.2–10.1)	9.5 (8.8–10.2)	.64
Platelets ($\times 10^9$/L), mean (95%CI)	150 (118–183)	233 (125–340)	130 (99–161)	.01
LDH (IU/L), mean (95%CI)	225 (207–244)	222 (160–285)	226 (207–245)	.88
CRP (mg/L), mean (95%CI)	17.4 (5.2–29.5)	70.2 (12.7–127.7)	4.4 (2.0–6.8)	<.01
IPSS score ≥ 1.5, n (%)	15 (24.6)	2 (16.7)	13 (26.5)	.71
Died during follow up, n (%)	13 (21.3)	5 (41.7)	8 (16.3)	.11

AIMs = autoimmune manifestations, CI = confidence interval, CRP = C-reactive protein, Hb = hemoglobin, IPSS = International Prognostic Scoring System, LDH = lactate dehydrogenase, MDS = myelodysplastic syndrome, MDS-U = myelodysplastic syndrome-unclassifiable, RAEB = refractory anemia with excess blasts, RARS = refractory anemia with ring sideroblasts, RCMD = refractory cytopenia with multilineage dysplasia, RCUD = refractory cytopenia with unilineage dysplasia, WBC = white blood cell.

* Calculated by Student's *t* test or Fisher's exact test.

Table 2

Treatments for MDS in patients with and without the AIMs.

	All patients (n = 61)	MDS with AIMs (n = 12)	MDS without AIMs (n = 49)	P*
Supportive care				
Transfusion, n (%)	20 (32.8)	2 (16.7)	18 (36.7)	.37
Anabolic steroid, n (%)	2 (3.3)	0 (0)	2 (4.1)	1.00
Hematopoietic growth factor				
G-CSF, n (%)	2 (3.3)	0 (0)	2 (4.1)	1.00
Epo, n (%)	7 (11.5)	0 (0)	7 (14.3)	.33
TPO-RA, n (%)	2 (3.3)	0 (0)	2 (4.1)	1.00
Immunosuppressive therapy				
PSL, n (%)	2 (3.3)	0 (0)	2 (4.1)	1.00
CsA, n (%)	4 (6.6)	1 (8.3)	3 (6.1)	1.00
Hypomethylating agent, n (%)	3 (4.9)	2 (16.7)	1 (2.0)	.10
Hematopoietic stem cell transplantation, n (%)	6 (9.8)	2 (16.7)	4 (8.2)	.33
Others				
Clinical trial, n (%)	1 (1.6)	0 (0)	1 (2.0)	1.00
No treatment, n (%)	31 (50.8)	8 (66.7)	23 (46.9)	.34

AIMs = autoimmune manifestations, CsA = cyclosporin A, Epo = erythropoietin, G-CSF = granulocyte-colony stimulating factor, MDS = myelodysplastic syndrome, PSL = prednisolone, TPO-RA = thrombopoietin-receptor agonist.

* Calculated by Fisher's exact test.

acute coronary syndrome in 2, 2, 1, 1, 1, and 1 patient, respectively. The univariate analysis showed that the presence of AIMs (HR 3.24, 95%CI 1.03–10.23, $P = .045$), karyotype abnormalities (intermediate vs good, HR 6.82, 95%CI 1.37–34.04, $P = .02$; poor vs good, HR 11.69, 95%CI 2.23–61.32, $P < .01$), and higher-risk disease according to the IPSS (HR 3.25, 95%CI 1.05–10.08, $P = .04$) were significantly associated with mortality (Table 3). The multivariate analysis showed that the presence of AIMs (HR 4.76, 95%CI 1.39–16.35, $P = .01$) and higher-risk disease according to the IPSS (HR 4.79, 95%CI 1.40–16.34, $P = .01$) were independently associated with the increased risk of mortality (Table 3).

3.5. Comparison of mortality in patients with MDS stratified according to the IPSS scores and AIMs

The currently utilized treatment algorithms for MDS are based on prognostic scoring systems such as the IPSS and not the WHO classification since the IPSS predicts prognosis more accurately than the WHO classification.[19] Therefore, to evaluate whether

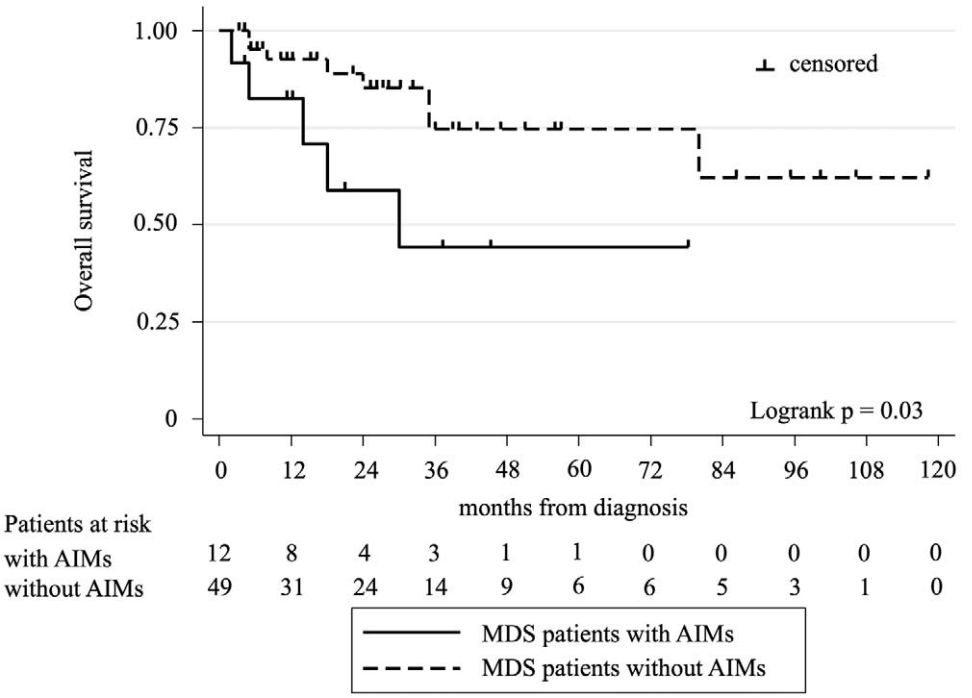

Figure 2. Kaplan–Meier survival curves of patients with or without the AIMs associated with MDS. There is a significant difference in the time to death between the 2 groups ($P = .03$ by the log-rank test).

Table 3

Univariate and multivariate Cox proportional hazards models for mortality in patients with MDS.

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age	1.00 (0.97–1.04)	.83	–	–
Gender; female vs male	0.32 (0.07–1.47)	.14	–	–
Karyotype			–	–
Intermediate vs good	6.82 (1.37–34.04)	.02	–	–
Poor vs good	11.69 (2.23–61.32)	<.01	–	–
Cytopenia; 2/3 vs 0/1 lineage	1.00 (0.33–2.98)	1.00	–	–
Bone marrow blasts (%)	0.95 (0.73–1.24)	.70	–	–
IPSS score; ≥1.5 vs <1.5	3.25 (1.05–10.08)	.04	4.79 (1.40–16.34)	.01
With AIMs vs without AIMs	3.24 (1.03–10.23)	.045	4.76 (1.39–16.35)	.01

AIMs = autoimmune manifestations, CI = confidence interval, HR = hazard ratio, IPSS = International Prognostic Scoring System.

the presence of AIMs was associated with the MDS prognosis independently of the IPSS risk classification, we divided patients into 4 groups to compare survival rates: higher-risk groups (IPSS ≥ 1.5) with or without the AIMs and lower-risk groups (IPSS < 1.5) with or without the AIMs (Fig. 3). In this grouping, only 2 patients were included in higher-risk group with the AIMs, so these patients were excluded from this analysis. The survival was worst in the higher-risk group without the AIMs. Surprisingly, the prognosis in the lower-risk group with the AIMs was comparable to that in the higher-risk group without the AIMs, and there was no statistically significant difference between these 2 groups ($P = .9$ by the log-rank test). Overall, these data suggested that AIMs should be considered as a poor prognostic factor independently of the IPSS risk group.

4. Discussion

In this retrospective study, the AIMs were identified in 20% of the patients with MDS. The increases in neutrophil counts and CRP levels observed in patients with the AIMs likely reflect latent neutrophilic inflammation in these patients. The prognosis was poor and comparable between those with the MDS-associated AIMs and those with high-risk MDS according to the IPSS, suggesting that the AIMs might be an independent prognostic factor in MDS.

The cause of the frequent development of AIMs in patients with MDS remains unclear, although the underlying immune dysregulation in MDS has long been considered a potential mechanism. The levels of various cytokines such as tumor necrosis factor α (TNF-α), interferon γ, transforming growth

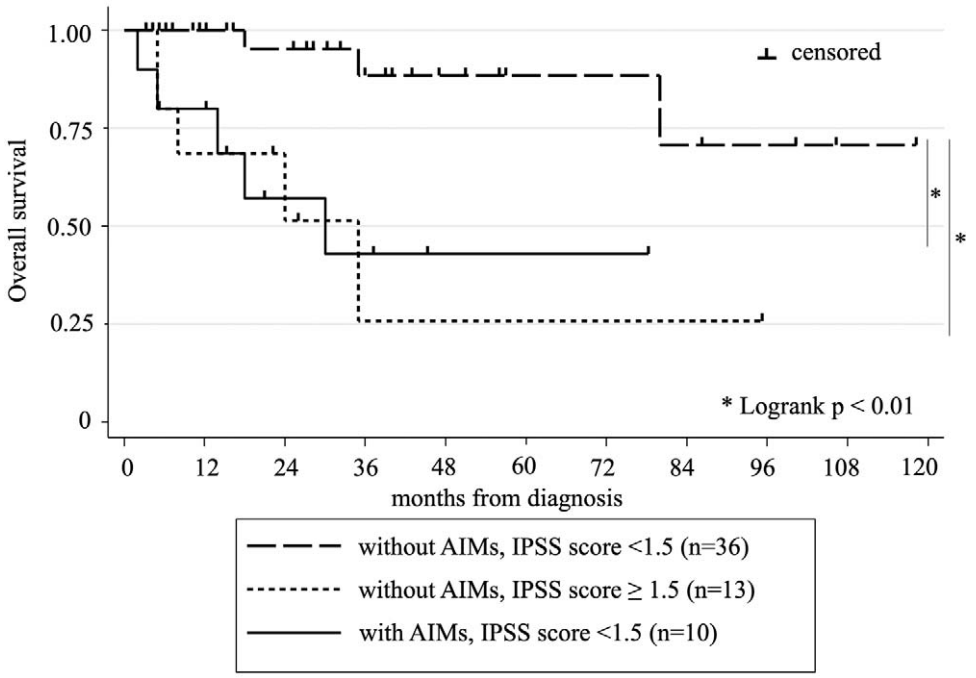

Figure 3. Kaplan–Meier survival curves of patients with MDS stratified according to the IPSS scores and AIMs. The prognosis in the group with lower-risk MDS and the AIMs is comparable to that in the group with higher-risk MDS without the AIMs, and there was no statistically significant difference between these 2 groups ($P = .9$ by the log-rank test).

factor β, and interleukin 6 have been found to be elevated in the peripheral blood and bone marrow of patients with MDS.[20] The clonal expansion of $CD8^+$ T cells have also been reported in patients with MDS harboring trisomy 8 who are more responsive to immunosuppressive therapies.[21] The impairment of regulatory T cell function has also been observed in early-stage MDS.[22] Conversely, the AIMs have been observed to precede the diagnosis of MDS. Kristinsson et al reported that a history of AIMs was associated with a two-fold increase in MDS risk and proposed that chronic immune activation might act as a trigger for the development of MDS.[23] These data collectively suggest that MDS can be both a cause and a consequence of the AIMs.

The treatment of MDS-associated AIMs is difficult since the underlying cytopenia and ineffective hematopoiesis in MDS can increase the risk of infectious complications. Steroids are the first-line treatment, and a complete response (CR) or partial response (PR) is achieved in 80% of cases.[13] However, despite the initial response, steroid dependence, or relapse often occurs, requiring second-line treatment. As second-line treatment, immunosuppressive drugs, such as cyclophosphamide, azathioprine, mycophenolate mofetil, and methotrexate, are used in combination with steroids. In a French multicenter retrospective study, Mekinian et al analyzed the efficacy of biologics (TNF-α inhibitors, tocilizumab, rituximab, and anakinra) and showed that the overall response (CR and PR) was more frequent (66%) with rituximab.[24] If MDS is the cause of AIMs, therapies used to treat MDS may simultaneously treat the AIMs. Fraison et al recently investigated the efficacy of azacitidine on the MDS-associated AIMs in 22 patients and reported that CR or PR was achieved in 86% of the cases.[25] The reduction or discontinuation of steroids and/or immunosuppressive drugs was also observed in most cases.

According to the current treatment approaches for MDS, patients with lower-risk MDS (IPSS < 1.5) are observed carefully without treatment or are treated with immunosuppressive drugs, cytokine therapy, and thalidomide analogues. Conversely, in patients with higher-risk MDS (IPSS ≥ 1.5), allogenic hematopoietic stem cell transplantation (HSCT) is considered as a first-line treatment.[19] In the current study, we demonstrated that MDS-associated AIMs were a poor prognostic factor, suggesting that intensive therapies might be considered in patients with MDS-associated AIMs, even among those with lower-risk MDS.

The limitations of our study were that the analyses were conducted retrospectively and the results were obtained from a small number of patients. A prospective study with large sample size is needed to confirm our results.

In conclusion, we demonstrated that AIMs predicted poor prognosis independently of IPSS. Treatment strategies for patients with MDS-associated AIMs should be reconsidered, even in those with low-risk MDS according to the IPSS.

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Author contributions

YA and YK participated in study conception and design. YA, YK, and KM participated in data acquisition and analysis. YA, YK, MA, YK, HM, MA, TM, TH, KA, and HN contributed to the interpretation of results. YA was a major contributor in writing the manuscript. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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