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Autoimmune diseases in myelodysplastic syndrome favors patients survival: A case control study and literature review

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ABSTRACT

Background: We conducted a monocentric retrospective study of patients with myelodysplastic syndromes (MDS) and autoimmune or inflammatory disorders (AIMs) and a literature review. We analyzed the association with subgroups of the WHO 2016 MDS classification and patient's survival in a case control study. Risk factors associated with survival were analyzed by uni- and multivariate analysis.

Results: From all MDS patients 11% presented with AIMs. These were heterogeneous and the most frequent where polyarthritis (25%) and autoimmune cytopenias (17%). No difference for frequency and type of AIMs was observed for the WHO 2016 MDS subgroups ($p = .3$). In the case control study WHO classification, karyotype abnormalities, IPSS-R and IPSS were similar in both groups. The overall survival from MDS diagnosis was better in the group with AIMs [10.3 ± 0.6 (IC95% 6.2–12.9) versus 4.8 ± 1.1 years (IC95% 4.2–8.7), $p = .04$]. The better survival was restricted to MDS with low or intermediate-1 IPSS [11.1 ± 1.5 (IC95% 9.9-NR) versus 8.7 ± 1.3 years (IC95% 4.8–10.3), $p = .006$]. The better survival was only observed when AIMs diagnosis was timely associated or appeared after MDS diagnosis ($p = .04$). Factors associated with a better overall survival and survival without AML were steroid dependence [respectively HR = 0.042, $p = .003$, (IC95% 0.005–0.33) and HR = 0.07, $p = .002$, (IC95% 0.013–0.39)], a diagnosis of AIMs and MDS timely associated [respectively HR = 0.05, $p = .009$, (IC95% 0.006–0.478) and HR = 0.1, $p = .008$, (IC95% 0.018–0.54)] or a diagnosis of AIMs after MDS [respectively HR = 0.024, $p = .009$, (IC95% 0.001–0.39) and HR = 0.04, $p = .008$, (IC95% 0.003–0.43)].

Conclusion: Autoimmune and inflammatory diseases associated to MDS are heterogeneous. AIMs diagnosed after or concomitantly to MDS seems associated with a better survival. Prospective studies are necessary to demonstrate that autoimmunity is associated to a better control of the MDS clone.

1. Introduction

Various autoimmune or inflammatory diseases (referred here as auto-immune and inflammatory manifestations, AIMs) have been associated to myelodysplastic syndromes (MDS), with a frequency ranging from 10 to 28% in previous reports [1].

The link between both conditions is not univocal. First autoimmune diseases have been associated to an increase risk of MDS with an OR ranging from 1.5 to 3.5 [2–4]. However this is mostly associated with autoimmune disease evolving from > 10 years and could be related to MDS complicating long term immunosuppressive therapy. On the other hand patients with MDS are at higher risk for AIMs, with and Odds ratio ranging from 4 to 5 [1]. In these cases there is a temporal association between both conditions. It is suspected that AIMs are induced by the MDS clone triggering and abnormal inflammatory or immune reaction. Local immune dysregulation at the medullary level would result in systemic manifestations through inappropriate immune cell activation and secretion of inflammatory cytokines. Along this dysregulation of T cells in MDS have been reported for Th17, Treg and LGL [5]. However the pathophysiological link between the myelodysplastic clone and AIMs and the impact of AIMs on patients outcome is not well established.

Abbreviations: AIMs, Auto-immune and Inflammatory manifestations; MDS, Myelodysplastic syndromes; CMML, Chronic myelomonocytic Leukemia

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For this reason we conducted a regional retrospective study to determine clinical features and outcomes of MDS patients with (MDS/AIM +) and without (MDS/AIM-) auto-inflammatory manifestations.

2. Patients and methods

2.1. Patients

Data were collected in a regional referral center for MDS and autoimmune and inflammatory diseases. Patient's clinical records between 2004 and April 2016 matching for AIMs and MDS were analyzed for inclusion in the study. Patients were included if 1) age ≥ 18 year 2) diagnosis of MDS or CMML on bone marrow aspiration 3) clinical AIMs. Patients were excluded if they were treated by immunosuppressant for AIMs before the diagnosis of MDS or CMML. Autoimmune hypothyroidism or isolated antinuclear auto-antibodies positivity without clinical manifestations were not considered as “clinical AIM” in this study.

MDS were diagnosed and classified according to WHO 2016 criteria [6] and stratified by IPSS [7] and IPSS-R [8] prognostic scores. AIMs were classified according to usual international classification criteria (for SLE using ACR criteria [9]; for systemic vasculitis the Chapel Hill vasculitis criteria [10]; for relapsing polychondritis using Michet criteria [11]; for Sjögren's syndrome using the American-European Consensus group criteria [12]; for Sweet's syndrome using Von Den Driesch criteria [13]. For analysis AIMs have been grouped according to preferential organ involvement: vasculitis, inflammatory arthritis, cutaneous manifestations, relapsing polychondritis (RP), cytopenias, coagulation disorders and other diseases. Clinical manifestations and biological parameters at diagnosis were retrospectively recorded.

The association of MDS and AIMs was considered concomitant if both diagnosis were timely associated (one year before or after MDS diagnosis), preceding MDS (> 1 years before MDS) or following MDS (> 1 years after MDS). The time of MDS diagnosis retained for the study was the date of bone marrow aspiration. AIMs treatments and their efficacy were analyzed retrospectively. Steroid efficacy was retained in case of improvement of clinical, biological and/or imagery AIMs manifestations. Steroid dependence was defined as a worsening of clinical, biological and/or imagery AIMs manifestations during steroid tapering or by the need of another immunosuppressive or biologic drug for AIMs.

A control group of 127 patients diagnosed with MDS without AIMs after a follow-up of > 2 years and followed in the same hematology department was used for the case-control study.

According to the current French Legislation (Loi Huriet-Sérusclat 88–1138, December 20, 1988, and its subsequent amendments, text available at {http://www.chu-toulouse.fr/IMG/pdf/loihuriet.pdf}), an observational study that does not change routine management of patients does not need to be declared or submitted to the opinion of a research ethics board.

2.2. Literature review methodology

Articles were selected on MEDLINE (National Library of Medicine, Bethesda, MD). The keywords used for the search were “myelodysplastic syndrome and autoimmunity” and “myelodysplastic syndrome and autoimmune disease”. Clinical articles in French or English language between 1981 and 2017 were considered for the review except pediatric cases, duplicates or those with < 10 patients.

2.3. Statistical analysis

Values of variables were given in mean or median (SD) or percentages (frequencies) accordingly. Survival was calculated from time of the diagnosis of MDS. Survivals were estimated according to Kaplan-Meier method and compared by the log-rank test. Univariate and multivariate analysis using Cox regression model was performed to identify prognostic factors associated with survival. A p-value < .05 was considered statistically significant.

Table 1
Frequency of AIMs in MDS patients.

	n	%
Polyarthritis	22	25
Immune cytopenias/caoagulation disorder	15	17
Vasculitis	11	12
Cutaneous manifestations	11	12
Relapsing polychondritis	6	7
Others	24	27

3. Results

3.1. Patients characteristics

3.1.1. AIMs characteristics

From the 801 patients with MDS 89 (11%) presented with AIMs. AIMs presented by MDS patients were polyarthritis in 25% (n = 22), immune cytopenias or coagulation disorders in 17% (n = 15), vasculitis or cutaneous manifestation in 12% (n = 11), relapsing polychondritis (RP) in 7% (n = 6) (Table 1). Cutaneous manifestation were: Sweet's syndromes (n = 7), psoriasis (n = 1), bullous dermatosis (n = 1), cutaneous lupus (n = 1), unclassified dermatose (n = 1). Other manifestations (27%, n = 24) were by frequency Sjögren's syndrome (n = 3), myasthenia gravis (n = 1), antiphospholipid syndrome (n = 1), CREST syndrome (n = 1), sarcoidosis (n = 1), pulmonary fibrosis (n = 1), unclassified pathology (fever, mediastinal adenopathy, rash and peripheral neuropathy) (n = 1).No difference was observed between frequencies of different AIMs manifestations according to the WHO classification subgroups (p = *.372*) (Table S1). The frequency of AIMs type, according to the classification by subgroups, was not different for AIMs occurring before, concomitantly or after the diagnosis of MDS (p = *.126*) and for AIMs occurring before and concomitantly or after the diagnosis of MDS (p = *.783*) (Table S2).

3.1.2. MDS characteristics

Characteristics of MDS for WHO 2016 classification, karyotype abnormalities, IPSS-R and IPSS were variable in patients with AIMs (Table 2). Both groups were comparable for IPSS-R (p = *.11*) or IPSS (p = *.43*).

3.2. Patients survival

Overall 40.9% of the MDS/AIM+ patients were dead at the end of follow-up versus 52% of the MDS/AIM- (p = *.13*). Follow-up was similar in both groups (respectively 3.7 and 3.9 years, p = *.84*). Overall survival from time to MDS diagnosis was better in MDS/AIM+ than in MDS/AIM- patients (respectively 10.3 ± 0.6 (IC95% 6.2–12.9) and 4.8 ± 1.1 years (IC95% 4.2–8.7), p = *.04*) (Fig. 1A). Comparing the survival depending on MDS risk stratification by IPSS we observed a better survival in the MDS/AIM+ with low or intermediate-1 IPSS (respectively 11.1 ± 1.5 (IC95% 9.9-NR) versus 8.7 ± 1.3 years (IC95% 4.8–10.3), p = *.006*) (Fig. 1B). There was no difference for high risk IPSS (p = *.6*).

Comparing the survival depending on MDS risk stratification with each IPSS-R no difference was observed. AIM can precede or follow MDS diagnosis. AIMs diagnosis was made before (> 1 year) in 20.7%, timely associated (< 1 year before and after MDS diagnosis) in 68.3%, or after MDS diagnosis (> 1 year) in 11%. The survival of patients with AIM before [6.2 ± 1.5 years (IC95%2.3-NR)], timely associated [10.3 +/− 1.4 years (IC95%5.7–11.1)] or after MDS diagnosis [21.1 +/− 2.6 years (IC95%5.4-NR)] was significatively different (p = *.04*) (Fig. 1C).

Table 2
Baseline characteristics of MDS/AIM + and MDS/AIM - patients.

		MDS/AIM+ $n = 89$ (%)	MDS/AIM- $n = 127$ (%)	p
Age	*(mean +/−SD)*	68,9 +/− 1,2	69,9 ± 1,1	0.28
Sex	Male	51 (57,3)	86 (67,7)	0.15
	Female	38 (42,7)	41 (32,3)	
WHO 2016	MDS-SLD	13 (14,6)	12 (9,4)	0.051
	MDS-MLD	21 (23,6)	18 (14,2)	
	MDS-EB-1	17 (19,1)	22 (17,3)	
	MDSEB-2	6 (6,7)	25 (19,7)	
	CMML-1	19 (21,3)	27 (21,3)	
	CMML-2	1 (1,1)	4 (3,1)	
	MDS-RS-SLD	6 (6,7)	10 (7,9)	
	MDS-RS-MLD	2 (2,2)	6 (4,7)	
	MDS-U	3 (3,4)	0 (0)	
	5q syndrome	1 (1,1)	3 (2,4)	
Karyotype	Normal	49 (65,3)	85 (66,9)	0.88
Karyotype	Very favorable	2 (2,7)	0 (0)	0.32
IPSS-R	Favorable	59 (78,7)	95 (74,8)	
	Intermediate	7 (9,3)	16 (12,6)	
	Poor	6 (8)	15 (11,8)	
	Very poor	1 (1,3)	1 (0,8)	
IPSS	Low	28 (40)	46 (36,2)	0.43
	Intermediate-1	28 (40)	45 (35,4)	
	Intermediate-2	11 (15,7)	22 (17,3)	
	High	3 (4,3)	14 (11)	
IPSS-R	Very low	7 (10)	21 (16,5)	0.11
	Low	39 (55,7)	45 (35,4)	
	Intermediate	12 (17,1)	29 (22,8)	
	High	7 (10)	21 (16,5)	
	Very high	5 (7,1)	11 (8,7)	
AML		13 (14,6)	35 (27,6)	**0.03**
Graft		9 (10,1)	12 (9,4)	1
Death		36 (40,9)	66 (52)	0.13
Follow-up	*(median, years)*	3,7	3,9	0.84

AML: acute myeloid leukemia; SD: standard derivation. Bold text corresponds to a p-value < 0.05

3.3. Time to AML and risk factors associated with survival

Survival without AML was comparable in both MDS/AIM + or – groups (respectively 10.7 ± 0.3 (IC95% 8.2-NR) versus 8.7 years (IC95% 7–12.9), $p = .39$. However time to AML was longer in MDS/AIMS+ than in controls (respectively 9.9 ± 2.3 (IC95% 5.6–11.1) versus 4.4 years ± 0.99 (IC95% 3.7–7.9) ($p = .04$). In the univariate analysis the only factor associated with a worse survival was patient's age. None of the AIM manifestation was separately associated to survival. The subgroup of AIM diagnosed after MDS, but not before or timely associated, was associated with a better survival of AIM after MDS diagnosis ($p = .02$)(Table 3).

In the multivariate analysis, patient's age was associated with worse overall survival [HR = 1.13, $p = .032$, (IC95% 1.01–1.28)]. Factors associated with a better overall survival and better survival without AML were a steroid dependence (respectively HR = 0.042, $p = .003$, (IC95% 0.005–0.33)] and [HR = 0.07, $p = .002$, (IC95% 0.013–0.39)], a diagnosis timely associated respectively HR = 0.05, $p = .009$, (IC95% 0.006–0.478)] and [HR =0.1, $p = .008$, (IC95% 0.018–0.54)] and a diagnosis of AIM after MDS diagnosis [respectively HR = 0.024, $p = .009$, (IC95% 0.001–0.39)] and [HR = 0.04, $p = .008$, (IC95% 0.003–0.43)].

3.4. AIMs associated to MDS: a literature review

The search by Medline on PubMed retrieved 755 publication. From these 729 non-clinical studies were excluded. Clinical studies with < 10 patients, lack of IPPS or IPSS-R score and absence of AIMs characterization were also excluded (see flowchart, Fig. S3).

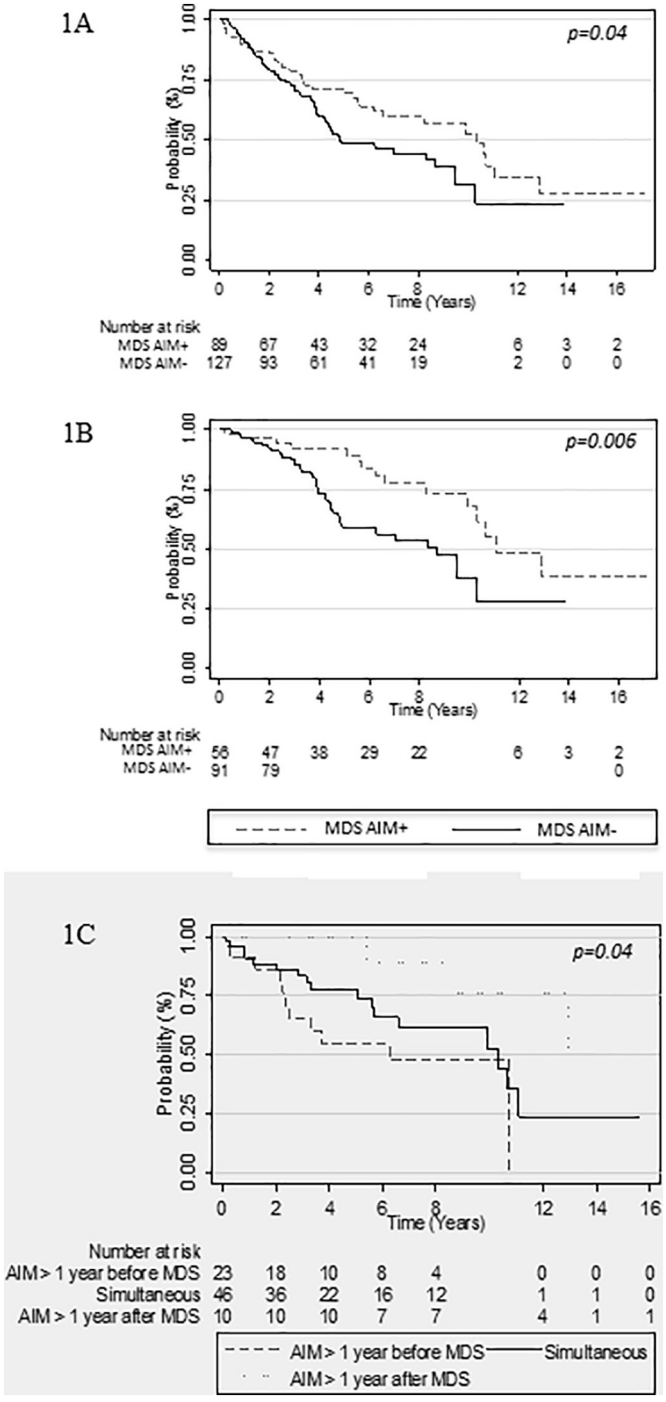

Fig. 1. Survival in MDS patients with our without AIM.
1A: Overall survival from time to MDS diagnosis with our without AIM, **1B:** Overall survival from time to MDS diagnosis in low and intermediate-1 IPSS score with our without AIM, **1C**: Survival in MDS with AIM depending on time of AIM appearance.

3.4.1. Characteristics of MDS associated to AIMs

Studies have failed to outline a consistent correlation between the type of MDS and AIMs. For example RA or RCMD WHO subtypes were more frequent in cases with AIMs in the study of Komrokji et al. [14] but Mekinian et al. reported a lower frequency of RARS in AIMs patients [15]. Hamidou et al. reported severe vasculitis associated with CMML [16] and the study of Mekinian reported an association of vasculitis and CMML [15]. We did not found such association. Table S4 reports the frequency of MDS subtypes and the respective AIMs

Table 3
Patients characteristics associated with survival in univariate analysis.

	HR	p	[IC95%]
Sex	0.69	0.09	0.45–1.05
Age	**1.03**	**0.01**	**1.01–1.05**
Steroid dependence	0.52	0.17	0.19–1.33
Response to treatment	0.66	0.46	0.22–1.96
AIMs manifestations			
Vasculitis	1		
Polyarthritis	0.80	0.72	0.2–2.68
Cutaneous manifestationss	1.26	0.75	0.31–5.18
Immune cytopenia	1.30	0.67	0.36–4.74
Relapsing polychondritis	1.17	0.84	0.26–5.29
Others	1.35	0.61	0.42–4.34
AIM diagnosis			
Before MDS	1		
Timely associated	0.61	0.2	0.28–1.31
After MDS	**0.2**	**0.02**	**0.05–0.77**

Bold text corresponds to a p-value < 0.05

frequency illustrating their variability in different series. In the same way none of the studies reported yet have shown a correlation between karyotype or gene mutations and AIMs, except for trisomy 8 and pseudo-Behcet disease that we did not observe here. Mekinian and colleagues reported a higher frequency of poor karyotypes in MDS/AIMs [15] that was not the case in this study. From the largest series two reported male [14,15] and one female [17] predominance in MDS/AIMs+ compared to MDS/AIMs-. We did not observe any difference for age and sex between both groups.

3.4.2. Characteristics of AIMs associated to MDS

Most frequent AIMs reported are vasculitis, neutrophilic dermatoses, and polyarthritis (see Fig. 2). However the rate of different AIMs vary between series and a significant part of these patients presented with unclassified AIMs as illustrated in Fig. 2. In Mekinian study only in 75 (66%) cases fulfilled the usual classification criteria [15].

3.4.2.1. Vasculitis. Frequency of vasculitis vary between 4 and 60% (Fig. 2). Vasculitis vary from isolated cutaneous vasculitis to severe systemic forms [16]. A significant association was shown between chronic myelomonocytic leukemia (CMML-1) and systemic vasculitis by some studies. Patients with vasculitis, independent of their type, were characterized by significantly more frequent renal involvement (microaneurysms or glomerulonephritis), steroid dependence, and uncomplete remission (Fain [18]). Most case are related to middle-size or small vessels vasculitis and Giant cell arteritis (GCA) has been reported only in few cases or series [19]. Because MDS and GCA appear at the same age this association could be fortuitous. Vasculitis seems to precede MDS as observed here [20,21].

3.4.2.2. Dermatoses. Most frequent cutaneous involvement is neutrophilic dermatosis observed in 4 to 36% of patient with AIMs (Fig. 2). Neutrophilic dermatosis has been shown in one study to be associated with an increased frequency of 5q deletion [22]. In newly diagnosed MDS patient a prospective study [23] has shown that adjusted for age and gender, the presence of skin findings (25%) is associated with an increased risk of severe MDS (OR 3.59; 95%CI, 1.18–10.92) [23]. Other cutaneous manifestations reported as AIMs were photosensitivity, prurigo nodularis, leucocytoclastic vasculitis and psoriasis however at a low frequency.

3.4.2.3. Arthritis. Most frequent is polyarthritis usually recognized as is undifferentiated arthritis. Some patients present with typical RA but the frequency of ACPA positivity reported is low [24]. The frequency of polymyalgia rheumatica and RS3PE syndrome is respectively 26% and 12% from a literature review [24]. Spondylarthritis has been rarely reported and was observed in two patients here.

3.4.2.4. Connective tissue disease. Connective tissue diseases have been

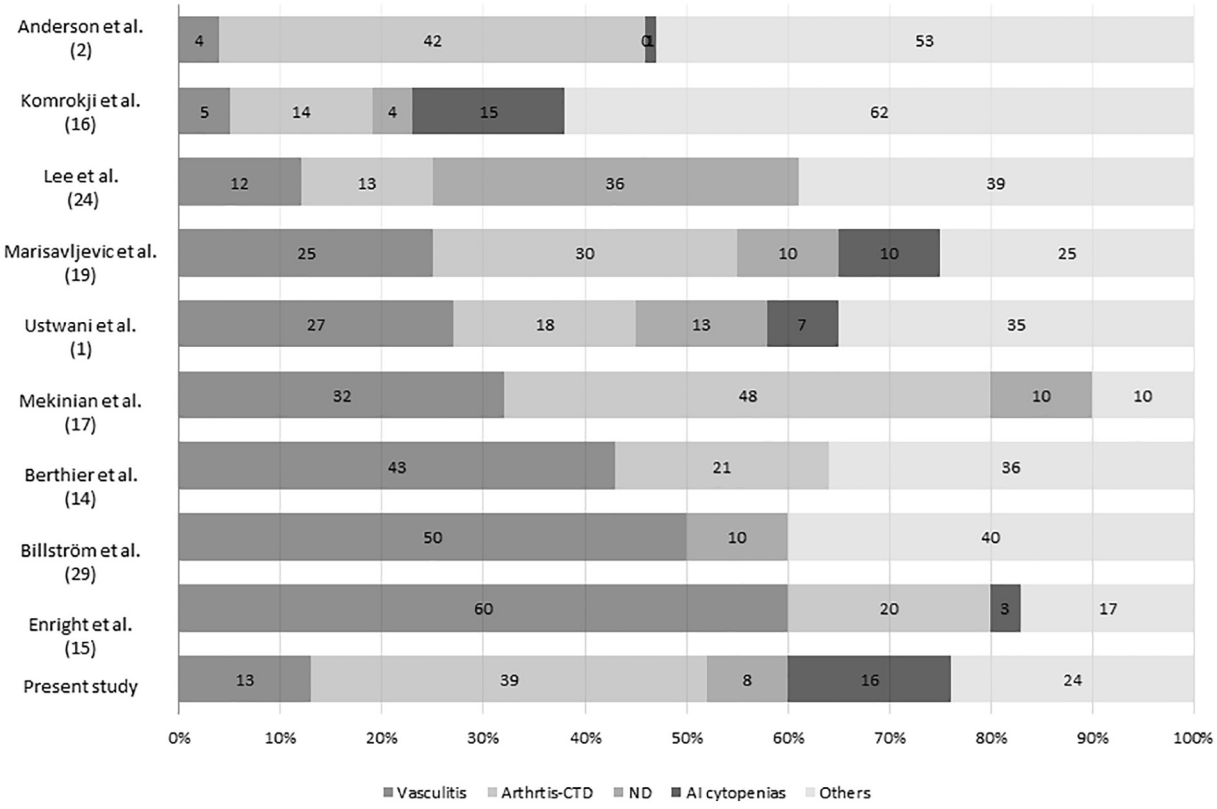

Fig. 2. Type and frequency of AIMs associated to MDS from different series.

Table 4
Studies analyzing the impact of AIMs in MDS patients survival.

Reference	Overall survival (months)	Impact on overall survival	Rate of AML	Follow-up (Month)
Mekinian et al. [15]	72 (IQR 59–105)	Not different from control group	22%	25 (IQR 12–58)
Komrokji et al. [14]	60 (IQR 50–70)	**Better for patients with AIM**	23%	74 (IQR 69–78)
Mekinian et al. [22]	NA	Not different from control group	ND	40.7 +/− 45.5 (mean, SD)
De Hollanda et al. ([20]	NA	Not different from control group	17.4%	ND
Marisavljevic et al. [17]	37	Not different from control group	ND	ND
Giannouli et al. [27]	NA	Not different from control group	15%	18
Billström et al. [28]	7	Not different from control group	ND	ND
Present study	**123**	**Better for patients with AIM**	**14.6%**	**44.4**

AML: acute myeloid leukemia; IQR: inter-quartile range; NA: non applicable; ND: not done; OS: overall survival; SD: standard derivation.

reported less frequently in MDS patients. In most cases autoimmune manifestations do not fulfill international classification criteria for autoimmune diseases. Some patients with characterized systemic lupus erythematosus, Sjögren's syndrome or myositis are reported but their frequency is low.

3.4.2.5. Treatments. Treatment of autoimmune manifestation in MDS is a challenge and in most studies steroid dependence and low rate of response to immunosuppressive drugs and biologic agent has been reported [25].In the literature steroid therapy was used in 50 to 100% of patients with AIMs with a high rate of dependence ranging from 32 to 66.6% of patients [15,26]. Azacitidine has been reported effective with 86% of response for AIMs associated to MDS but prospective studies are needed. Biologics were evaluated recently from a retrospective cohort reporting 66% of response to rituximab and a global response of 33% of patients to others biologics (anti TNF, anti-IL1 and anti-IL6). [25]

3.4.3. Impact of AIMs on patients with MDS survival

The impact of AIMs on patient's overall survival in MDS has been addressed by several case-control studies (Table 4). Most of these were retrospective and found no difference in the MDS/AIMs+ group [15,17,20,22,26–28].. The study of Komrokji et al. on a large retrospective cohort of MDS patient showed, as here, a better overall survival in MDS/AIM+ patients with a lower rate of AML transformation [14]. In this study autoimmune disease was an independent factor to the overall survival in a multivariate analysis, adjusting for revised IPSS and age > 60 years. In the contrary some AIMS as systemic vasculitis and/or cryoglobulinemic vasculitis and neutrophilic dermatosis have been associated in two separate studies with a worse prognosis [20,22]. One potentially important issue is the timely association between both conditions that has been scarcely studied and reported with some discrepancies. Some studies report cases of AIMs occurring before MDS in as much as 71.5% of patients while others report either 50% of patient presenting timely association of both diseases or AIMs occurring after MDS diagnosis in the majority of cases [1,26].

4. Discussion

A subset of patients with MDS present with autoimmune or inflammatory manifestations. This association raises several questions beside the pathophysiological and therapeutic aspects. These can be listed as following: what is the frequency and the clinical characteristics of different AIMs? Are AIMs associated to MDS different from classical auto-immune and inflammatory conditions? What is the type of MDS associated to AIMs? What is the prognosis of MDS patients with AIMs?

In our study, 11% of MDS patients presented with AIMs that is in the range, from 7 to 28%, of previous studies [14,17].Of note we excluded patients with previous immunosuppressive treatment for AIMs to avoid secondary MDS. We also excluded thyroiditis as AIMs because of its frequency in the general population. This could explain a relative lower frequency than that reported by some previous studies [18]. As reported here and in previous retrospective or prospective studies, the type of AIMs are very diverse. AIMs observed in our series, mainly vasculitis, polyarthritis, cutaneous manifestations, immune cytopenias and relapsing polychondritis encompass the range of conditions already reported [14,17]. We did not observed manifestations evocative of Behcet disease in patient with trisomy 8 as reported previously [10,15]. The interpretation of variations of frequencies of different AIMs is uneasy and could be related to patient selection bias from different centers. However four subtypes of AIMs: vasculitis, neutrophilic dermatoses, polyarthritis and immune cytopenias have been consistently documented as the most frequent manifestations. The rate of immune cytopenias was notably high in our series compared to other. We think that autoimmune cytopenia is underestimated in most series because it is difficult to distinguish from central cytopenia in MDS patients. Another point to underline is the great proportion of cases for which, according to current international classifications criteria's for AIMs, classification was uneasy because either typical pathological or biological markers were absent (Fain et al. [18] found 20% ANCA-positivity in MDS patients with vasculitis; Mekinian et al. [24] found 12/49 (24%) rheumatoid factor positivity in MDS patients with arthritis. This has been underlined by authors in several reports and a large proportion of patients are recognized as having unclassified connective disease [15]. Relapsing polychondritis is probably apart with a strong associations of severe forms with MDS [29].The variety of autoimmune and inflammatory conditions suggests that immune dysregulation in MDS is large and heterogeneous. Immune dysregulation and inflammation has been shown in the pathogenesis of MDS and T cell changes have been associated with MDS severity stages. Both Treg and Th17 subsets implicated in autoimmunity are modified in MDS patients. A pattern prone to license autoimmunity is precisely harbored by low risk MDS patients [5,30]. Regulatory CD4 T cells function are impaired in early stages of MDS and correlate with bone marrow blast infiltration and IPSS score. Conversely Th17 cells are overrepresented in low risk compared to high risk MDS and negatively correlate with Treg. Treg function and bone marrow homing is impaired and could favorize AIMs [31].

Because MDS encompass a variety of cytological, clonal and epigenetic diversity it is attempting to associate subtype of AIMs with subtype of MDS. It has been suggested that CMML is more frequently associated with AIMs but we found no significant association and in the largest case series CMML frequency (median 4%; range 2 to 27%) was not associated with vasculitis frequency (median 24; range 4 to 32%) [1,2,14,15,17]. Here we presented for the first time MDS classification on a large case series by the OMS 2016 scale. The most frequent OMS type observed accounting for > 75% of patients were MDS-MLD (23.6%), CMML-1 (21.3%), MDS-EB-1 (19.1%), MDS-SLD (14.6%). The frequency of each OMS 2016 subtype, the IPPS, IPSS-R or karyotype scoring were comparable with the control MDS/AIMs- group suggesting, as in other reports, that there is no correlation of a specific MDS type with AIMs. Only the frequency of AML was found significantly

higher in the MDS/AIMs- group despite a similar follow-up duration.

We observed that the overall survival was higher in the MDS/AIM+ group compared to the MDS/AIM- group. Only few case control studies have analyzed the impact of AIMs on the survival in MDS [14,15,17,20,22,26,27]. In six of these there was no difference observed between AIMs + or – groups. However in these reports the follow up was usually limited (median 25 range 18 to 44) and the number of patients with AIMs low (< 50) except in two studies. In a large retrospective study of 1408 MDS patients (with a frequency of AIMs of 28%). Komrokji et al. also observed a better survival of AIMs+ patients [14]. This suggests a protective effect of AIMs on MDS survival. Mekinian et al. also noted that despite worse baseline prognostic factors in MDS/AIMs+ patients the overall survival was similar than in the AIMs- group [15]. Discrepancies between these studies could be explained by several factors including the median follow-up duration. In the study of Komrokji et al. [14] and ours the follow-up was the longest, respectively 74 and 44 months. Moreover median age of patients, percentage of MDS/CMML subtypes, type of AIMs and the overall survival vary significantly between the different studies and probably impact patient's survival. Unfortunately we could not analyze the causes of death. Of note we observed a significantly higher global survival (median 123 month) than in all other studies. Factors that could explain this result were 1) a high rate of IPSS low and intermediate 1 risk patients (80%) and conversely more patients with normal or favorable karyotype 2) a lower median age of patients than in other studies 3) the absence of therapy related MDS known to have a worse prognosis 4) a relatively low rate of neutrophilic dermatosis (7/89) shown to be associated with poor survival [30]. The rate of AML was comparable with most other series but much higher than the 4% observed by Komrokji et al. [14].

The more favorable outcome of patient with AIMs was not associated with differences in the MDS or AIMs characteristics between both groups but with significantly higher rate of AML in patients without AIMs as in the study of Komrokji et al. [14]. The difference for survival was only observed in the IPSS very low, low and intermediate group but not the IPSS high or very risk.

The analysis of risk factors associated to survival did not individualize a group of AIMs but the timely association between MDS and AIMs. Only AIMs appearing after MDS diagnosis were associated with a better prognosis (HR 0.2). This difference was not associated with significant changes of AIMs type in our study between AIMs before, timely associated or after patients as reported by Lee et al. [22]. However the rate of relapsing chondritis and lung involvement was higher in patients with AIMs before. This observation could indicate that AIMs appearing after MDS diagnosis is induced by anti-tumor immunity and that in other cases the mechanism inducing autoimmunity or inflammation is different (i.e. bystander immune response) and therefore not associated to the control of the tumoral clone. The priming of an autoimmune disease by tumor antigen and the anti-tumor response has been described for rare forms of systemic sclerosis and could be one of the mechanisms of AIMs associated to MDS [32]. At a first step it would be interesting to analyze the correlation of bone marrow somatic mutations by NGS in MDS with the frequency and the type of AIMs.

5. Conclusion

In conclusion we present here the results of a case control study of MDS patients with or without AIMs. The main limitation of this study is the retrospective design. Patient where all characterized for MDS by a referral cytologist and autoimmune and inflammatory manifestations were classified by specialists. The major result is to show that patient with AIMS have a better outcome and that this is the case for patients with low and intermediate IPPS risk presenting with AIMs after MDs diagnosis. The rate of AML was higher in the absence of AIMs. We found no correlation between subsets of MDS and AIMs. AIMs were variable and often difficult to classify. Further studies are needed to elucidate the link between these pathologies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2018.07.009.

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