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Original article

Systemic inflammatory and autoimmune manifestations associated with myelodysplastic syndromes and chronic myelomonocytic leukaemia: a French multicentre retrospective study

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Abstract

Objective. We describe myelodysplastic syndrome (MDS)–associated systemic inflammatory and autoimmune diseases (SIADs), their treatments and outcomes and the impact of SIADs on overall survival in a French multicentre retrospective study.

Methods. In this study, 123 patients with MDS and SIADs were analysed.

Results. Mean age was 70 years (S.D. 13) and the male:female ratio was 2. The SIADs were systemic vasculitis in 39 (32%) cases, CTD in 31 (25%) cases, inflammatory arthritis in 28 (23%) cases, a neutrophilic disorder in 12 (10%) cases and unclassified in 13 cases (11%). The SIADs fulfilled the usual classification criteria in 75 (66%) cases, while complete criteria were not reached in 21 (19%) cases. A significant association was shown between chronic myelomonocytic leukaemia (CMML) and systemic

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CLINICAL SCIENCE

vasculitis ($P = 0.0024$). One hundred and eighteen (96%) SIAD patients were treated (91% with steroids), with an 83% response to first-line treatment, including 80% for steroids alone. A second-line treatment for SIADs was required for steroid dependence or relapse in 48% of cases. The effect of MDS treatment on SIADs could be assessed in 11 patients treated with azacytidine and SIAD response was achieved in 9/11 (80%) and 6/11 (55%) patients at 3 and 6 months, respectively. Compared with 665 MDS/CMML patients without SIADs, MDS/CMML patients with SIADs were younger ($P < 0.01$), male ($P = 0.03$), less often had refractory anaemia with ring sideroblasts ($P < 0.01$), more often had a poor karyotype (16% *vs* 11%, $P = 0.04$) and less frequently belonged to low and intermediate-1 International Prognostic Scoring System categories, but no survival difference was seen between patients with MDS-associated SIADs and without SIADs ($P = 0.5$).

Conclusion. The spectrum of SIADs associated to MDS is heterogeneous, steroid sensitive, but often steroid dependent.

Key words: myelodysplastic syndrome, autoimmune disorders, treatment, outcome.

Rheumatology key messages

- Myelodysplastic syndrome associated with autoimmune diseases has less favourable haematological features but similar outcome to myelodysplastic syndrome without systemic inflammatory or autoimmune diseases.
- Myelodysplastic syndrome-associated autoimmune diseases respond to steroids but have a high rate of steroid dependence.
- Preliminary findings suggest that myelodysplastic syndrome drugs, especially azacitidine, may have an effect on systemic inflammatory or autoimmune disease symptoms.

Introduction

Myelodysplastic syndrome (MDS) and chronic myelomonocytic leukaemia (CMML) are hematopoietic stem cell malignancies characterized by ineffective and dysplastic haematopoiesis leading to blood cytopenias and by a high risk of progression to acute myeloid leukaemia (AML) [1]. Systemic inflammatory and autoimmune diseases (SIADs) occur in 10–20% of patients with MDS or CMML [2]. Few reports have described MDS/CMML-associated SIADs, and the impact of SIADs on MDS outcome remains controversial [3, 5–9]. We showed previously that inflammatory arthritis in MDS/CMML patients is generally poorly controlled, with high rates of steroid dependence, while the use of steroid-sparing agents has been rarely reported [10]. We conducted a nationwide retrospective study to describe the different types of SIADs associated with MDS, the characteristics of the associated MDS/CMML and the outcomes of both disorders.

Patients and methods

Patient selection

We retrospectively collected data for patients with both MDS/CMML and SIADs diagnosed between 1993 and 2013 in 26 French centres. Physicians were asked by the Société Francaise de Médecine Interne, the Club Rhumatismes Inflammation and the Groupe Francophone des Myélodysplasies to report cases of SIADs with MDS or CMML and data were extracted from medical files by E.G. and A.M. Inclusion criteria were as follows: MDS or CMML according to the 2008 World Health Organization classification and previous, concomitant or successive occurrence of systemic inflammatory or autoimmune manifestations. Exclusion criteria included immunosuppressive treatment administered at least 12 months before MDS/CMML diagnosis and infectious, drug-related or neoplasm-related inflammatory systemic diseases. The study was approved by an institutional review board (Comité de Protection des Personnes, Aulnay sous Bois, Ile de France). Several patients with inflammatory arthritis ($n = 22$) presented in this case series have been published in a previous work [10].

MDS and CMML

The diagnosis of MDS and CMML was based on blood and bone marrow examination and were classified according to WHO 2008 criteria. Marrow karyotype was available in 83 patients. Patients were classified using the International Prognostic Scoring System (IPSS), low and intermediate-1 IPSS groups being combined in lower risk (IPSS 0–1) and intermediate-2 and high-risk MDS groups combined in higher risk (IPSS $\geqslant 1.5$) [11]. Response to treatment administered for MDS and CMML was assessed by International Working Group 2006 criteria [4] and specific criteria for CMML [12].

Systemic inflammatory and autoimmune diseases

Inflammatory and autoimmune manifestations were recorded for the following organs at the time of SIAD diagnosis and during follow-up: constitutional symptoms and non-infectious fever; lung, ENT, kidney, nervous system, skin, joint, eye or heart involvement and the presence of venous/arterial thrombosis. Laboratory data were recorded as follows (if available): platelets, blood tests,

serum creatinine, liver enzymes, ESR, CRP, fibrinogen, ANA, complement system (CH50, C3, C4), ANCA, cryoglobulinaemia, RF, ACPA, aPL, HIV, HVB and HVC serology.

For each patient, the inflammatory and autoimmune features (as previously determined by organ impairment) with biological, immunological, radiological and histological data were classified according to the usual international diagnostic criteria (per SLE using ACR criteria). Systemic vasculitis was classified according to the Chapel Hill vasculitis criteria [13]. When complete diagnostic criteria were not available, SIAD diagnosis was considered incomplete (per suspected SLE with three of four ACR criteria) and unclassified in the cases where it could not be classified among SIAD types.

Response to the treatment of SIADs was evaluated based on clinical, immunological, biological and radiological criteria. Complete response was defined as the complete disappearance of clinical features present at baseline, biological response as the normalization of acute phase reactants and immunological response as the normalization of immunological parameters, if applicable. Partial response was defined as a $\geqslant$50% improvement of the clinical, biological and immunological parameters. Steroid dependence was defined as a prednisone equivalent amount $>$20 mg/day during at least 2 months. SIAD diagnosis was considered concomitant with MDS when the diagnosis of both diseases was made within ±3 months and as before or after MDS in the remaining cases. Only cases of SIAD and MDS diagnoses within the previous 5 years were included in the study.

Control group

The control group consisted of 665 patients with MDS or CMML without any systemic inflammatory or autoimmune features prospectively followed during the 2003–13 period in the haematology department of Avicenne Hospital (Paris 13 University) and included in the Groupe Francophone des Myélodysplasies registry of MDS/CMML.

Statistical analysis

Descriptive statistics included the mean, standard deviation, median and interquartile ranges for continuous variables and frequencies (percentages) for categorical variables. To account for missing data, results were expressed as observed data (missing data were not replaced). A chi-square test or Fisher's exact test was used to compare categorical variables, and if normality was verified, Student's *t*-test was used to compare continuous variables.

Survival was defined from the MDS diagnosis and analysed using variables that can affect survival in MDS and compared in MDS patients with and without SIAD. Because of the high percentage of censored data, sensitivity analyses were done excluding patients lost to follow-up or taking into account only patients who died. These sensitivity analyses showed findings similar to the main analysis.

A univariate (Cox proportional hazard regression models or Kaplan–Meier) and a multivariate analysis of survival by a Cox regression model with stepwise selection were carried out to identify prognostic factors of survival (at the 5% level). A *P*-value $<$5% was considered significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). In addition to this primary analysis, a sensitivity analysis was performed with matching patients for sex and IPSS (one MDS patient with SIAD matched with five MDS patients without SIAD).

Results

MDS and CMML baseline characteristics and treatment

One hundred twenty-three patients (41 females and 82 males) with MDS/CMML and SIAD were included [median age 74 years (IQR 62–79)]. MDS/CMML characteristics (WHO classification, cytogenetics and IPSS) at the time of the MDS/CMML diagnosis are shown in Table 1. The most frequent subtypes were refractory cytopenia with multilineage dysplasia (26%), refractory anaemia with excess blasts 1 (RAEB-1) (15%) and CMML-1 (16%). The patients had the following karyotypes: normal ($n=53$), trisomy 8 ($n=3$), del (5q) ($n=6$), del (20q) ($n=3$), del (3q or 3p) ($n=3$), del (Y) ($n=2$), del (21 p) ($n=1$), various translocations ($n=4$) and complex karyotypes ($n=8$). Most patients had favourable karyotypes (75%) and the IPSS distribution was low (23%), intermediate-1 (int-1, 49%), intermediate-2 (int-2, 19%) and high (7%). Disease-modifying treatment for MDS/CMML was initiated in 47/111 cases (43%) 0.4–20 months (median 5 months) after the MDS/CMML diagnosis. First-line MDS treatment consisted in azacytidine [$n=13$ (28%)], decitabine [$n=6$ (13%)], hydroxyurea [$n=15$ (32%)], immunomodulatory derivatives of thalidomide [iMIDs; $n=5$ (11%), lenalidomide in four cases] and others [$n=8$ (17%), including ciclosporin and intensive chemotherapy]. Complete or partial haematological response to first-line treatment was noted in 18/43 cases among 47 patients with available data to analyse the treatment response (42%).

The control group of MDS/CMML patients without SIADs consisted of 665 patients (291 females and 374 males) with a median age of 75 years (IQR 24–95) (Table 1). Compared with MDS/CMML patients without SIADs, MDS/CMML patients with SIADs were younger ($P<0.01$), more frequently males ($P=0.03$), less often had refractory anaemia with ring sideroblasts (RARS) ($P<0.01$), more often had a poor karyotype (16% *vs* 11%, $P=0.04$) and less frequently belonged to the low and intermediate-1 IPSS categories (23% *vs* 34% and 19% *vs* 33%, respectively) (Table 1).

Associated inflammatory *and* autoimmune disease characteristics

The diagnosis of SIAD and MDS were concomitant in 38 (31%) cases, preceded MDS in 46 (37%) cases and occurred after the MDS diagnosis in 39 (32%) cases, with a mean 8.6 months (S.D. 52) between the diagnosis of the two diseases. SIADs were classified as systemic

Table 1 Baseline characteristics of patients with MDS/CMML-associated SIADs and MDS/CMML without SIADs

Characteristic	MDS/CMML with SIAD ($n = 123$)	MDS/CMML without SIAD ($n = 665$)
Age, mean (S.D.), years	70 (13)	73 (11)*
Female/male, *n* (%)	41/82 (50%)	291/374 (78%)*
Karyotype, *n* (%)		
Favourable	62 (75)	386 (69)
Intermediate	8 (10)	111 (20)*
Poor	13 (16)	64 (11)*
Bone marrow blasts, *n* (%)	6.5 (9)	4 (5)*
Peripheral blasts, *n* (%)	1.1 (4)	1.2 (5)
IPSS, *n* (%)		
Low	18 (23)	190 (34)*
Intermediate-1	39 (49)	181 (33)*
Intermediate-2	15 (19)	107 (19)
Poor	7 (9)	76 (14)
RCUD, *n* (%)	11 (9)	73 (11)
RARS, *n* (%)	1 (1)	57 (9)*
RAEB-1, *n* (%)	18 (15)	130 (20)
RAEB-2, *n* (%)	10 (8)	116 (17)*
CMML-1/2, *n* (%)	19(16)/5 (4)	96 (14)/7 (1)
5q syndrome, *n* (%)	6 (5)	25 (4)
RCMD, *n* (%)	31 (26)	136 (20)
MDS-U, *n* (%)	11 (9)	22 (3)
Progression to acute leukaemia, *n* (%)	26 (22)	83 (21)
Survival, median (IQR), months	72 (59–105)	75 (48–300)
Number of deaths, *n* (%)	43 (44)	154 (47)
Follow-up, median (IQR), months	25 (12–58)	25 (12–46)

*$P < 0.05$ (a chi-square test was used to compare categorical variables and Student's *t*-test was used to compare continuous variables). $P > 0.05$ for all other values. CMML: chronic myelomonocytic leukaemia; IPSS: International Prognostic Scoring System; IQR: interquartile range; MDS: myelodysplastic syndrome; MDS-U: unclassified MDS; RAEB: refractory anaemia with excess blasts; RARS: refractory anaemia with ring sideroblasts; RCMD: refractory cytopenia with multilineage dysplasia; RCUD: refractory cytopenia with unilineage dysplasia; SIAD: systemic inflammatory and autoimmune disease.

vasculitis in 39 cases (32%), CTD in 31 cases (25%), inflammatory arthritis in 28 cases (23%), neutrophilic disease in 12 cases (10%) and unclassified in 13 cases (11%). The different subtypes of SIADs among these groups are summarized in Table 2. Among the vasculitis diseases, polyarteritis nodosa and GCA were most frequent, while relapsing polychondritis and SLE were the most frequent among CTDs. Neutrophilic diseases were Sweet's syndrome ($n = 9$), pyoderma gangrenosum ($n = 2$) and aseptic abscesses ($n = 1$). In patients with inflammatory arthritis, the subtypes were PMR, RA, relapsing seronegative polyarthritis with oedema syndrome and undifferentiated arthritis. Within these groups, SIADs fulfilled the usual classification criteria in 75 (66%) cases, while complete diagnostic criteria were not found in 21 (19%) cases and available data were insufficient to completely check the diagnostic criteria in 17 (15%) cases. Cases with incomplete diagnostic criteria [$n = 21$ (19%)] included SLE, Behçet's disease and relapsing polychondritis.

At the time of SIAD diagnosis, the main clinical manifestations consisted of non-infectious fever with constitutional symptoms [$n = 43$ (35%)], skin [$n = 68$ (55%)], joint [$n = 84$ (68%)], lung [$n = 18$ (15%)], ENT [$n = 30$ (24%)], peripheral nervous system [$n = 14$ (11%)], kidney [$n = 12$ (10%)] and ocular involvement [$n = 18$ (15%)]. A history of venous thrombosis was present in 15 cases (12%). The number of involved organs at the diagnosis of SIAD was 2.6 (S.D. 1.5). ANA was present in 25/108 cases (23%), at a mean titre of 560 IU (S.D. 411); specific ENA in 3 cases (anti-SSA and anti-nucleosome antibodies) and positive anti-sDNA in 2 cases. ANCA was present in 8/95 (8%) cases (pANCA-MPO in 3 cases, cANCA-PR3 in 2 cases and without ELISA specificity in 3 cases). RF was found in 12/89 (13.5%) cases, with ACPA present in 5 cases, and cryoglobulinaemia in 5/56 cases (9%). Angiotensin-converting enzyme was normal in all 22 tested cases and mean serum gammaglobulin levels were 13 g/l (S.D. 5). aPL was detected in 17/61 cases (28%), including LA ($n = 2$), aCL ($n = 12$) and anti-β2GPI antibodies ($n = 7$). The CH50 level was 112% (S.D. 34; normal >100%) with C4 at 299 mg/l (S.D. 190; normal >200 mg/l) and C3 at 1043 mg/l (S.D. 328; normal >900 mg/l). At least one biopsy was performed in 67 cases (mostly skin, kidney, temporal artery and neuromuscular sites), showing positive results in 47 cases (70%). Articular erosions were noted in 2 (5%) of the 39 cases where bone X-rays could be reviewed.

The only correlation between WHO classification of MDS/CMML and type of SIAD was CMML type 1, which was more frequent in patients with systemic vasculitis than with other SIAD subtypes (29% *vs* 7%; $P = 0.0024$) (Table 3). Four of the six patients with Behçet's disease have trisomy 8, compared with only 4/79 patients with other SIADs ($P = 0.003$). Compared with higher-risk MDS (IPSS int-2 or high; $n = 20$), SIADs associated with lower-risk MDS (IPSS low or int-1; $n = 49$) were more frequently CTDs (29% *vs* 5%; $P = 0.05$), whereas neutrophilic diseases tended to be more frequent in patients with higher-risk MDS (25% *vs* 45%; $P = 0.06$), with a similar frequency of vasculitis.

Outcome of *SIADs*

One hundred and eighteen patients (96%) received specific treatment for SIADs. The mean number of different immunosuppressive treatments used for SIADs was 1.8 (S.D. 0.6). First-line treatment consisted of steroids in 91% cases, combined in 24% with other drugs, mainly HCQ. Various treatment regimens administered and their outcomes are shown in Fig. 1. Overall response to first-line treatment was observed in 83% of cases, including 80% for steroids alone. A second-line treatment was required for steroid dependence or relapse in 48% of

Table 2 Different types of MDS/CMML-associated SIAD

Group	*n* (%) (95% CI)	Type, *n*	Insufficient data, *n*	Incomplete criteria, *n*
Systemic vasculitis	39 (32) (23, 40)	Polyarteritis nodosa, 12 GCA, 9 Behçet's disease, 6 Cryoglobulinaemia, 3 GPA, 1 Unclassified, 8	Polyarteritis nodosa, 7 Unclassified, 7	Behçet's disease, 6 Polyarteritis nodosa, 1
CTDs	31 (25) (18, 33)	RP, 14 SLE, 8 Primary APS, 4 Myositis, 3 SS, 2	SS, 1 Myositis, 1	SLE, 8 RP, 6
Neutrophilic dermatosis	12 (10) (5, 15)	Aseptic abscesses, 1 Sweet's syndrome, 9 Pyoderma gangrenosum, 2	1	0
Inflammatory arthritis	28 (23) (15, 30)	PMR, 10 RA, 4 RS3PO, 4 Undifferentiated, 10	0	0
Unclassified	13 (11)	—	0	—

CMML: chronic myelomonocytic leukaemia; GPA: granulomatosis with polyangiitis; MDS: myelodysplastic syndrome; RP: relapsing polychondritis; RS3PO: remitting seronegative symmetrical synovitis with pitting oedema; SIAD: systemic inflammatory and autoimmune diseases.

Table 3 MDS subtypes in different types of SIAD

MDS subtype	CTDs (*n* = 28)	Neutrophilic diseases (*n* = 12)	Inflammatory arthritis (*n* = 27)	Systemic vasculitis (*n* = 33)
RCUD, *n* (%)	5 (18)	0	2 (7)	3 (9)
RAEB-1, *n* (%)	6 (21)	3 (25)	4 (15)	4 (12)
RAEB-2, *n* (%)	0	2 (17)	4 (15)	3 (9)
CMML-1/2, *n* (%)	2 (7)/0	1 (8)/1 (8)	2 (7)/2 (7)	11 (33)/2 (6)
RCMD, *n* (%)	7 (25)	3 (25)	9 (33)	8 (24)
5q syndrome, *n* (%)	2 (7)	0	3 (11)	1 (3)
Unclassified, *n* (%)	5 (18)	2 (17)	1 (4)	1 (3)

CMML: chronic myelomonocytic leukaemia; MDS: myelodysplastic syndrome; RAEB: refractory anaemia with excess blasts; RCMD: refractory cytopenia with multilineage dysplasia; RCUD: refractory cytopenia with unilineage dysplasia; SIAD: systemic inflammatory and autoimmune disease.

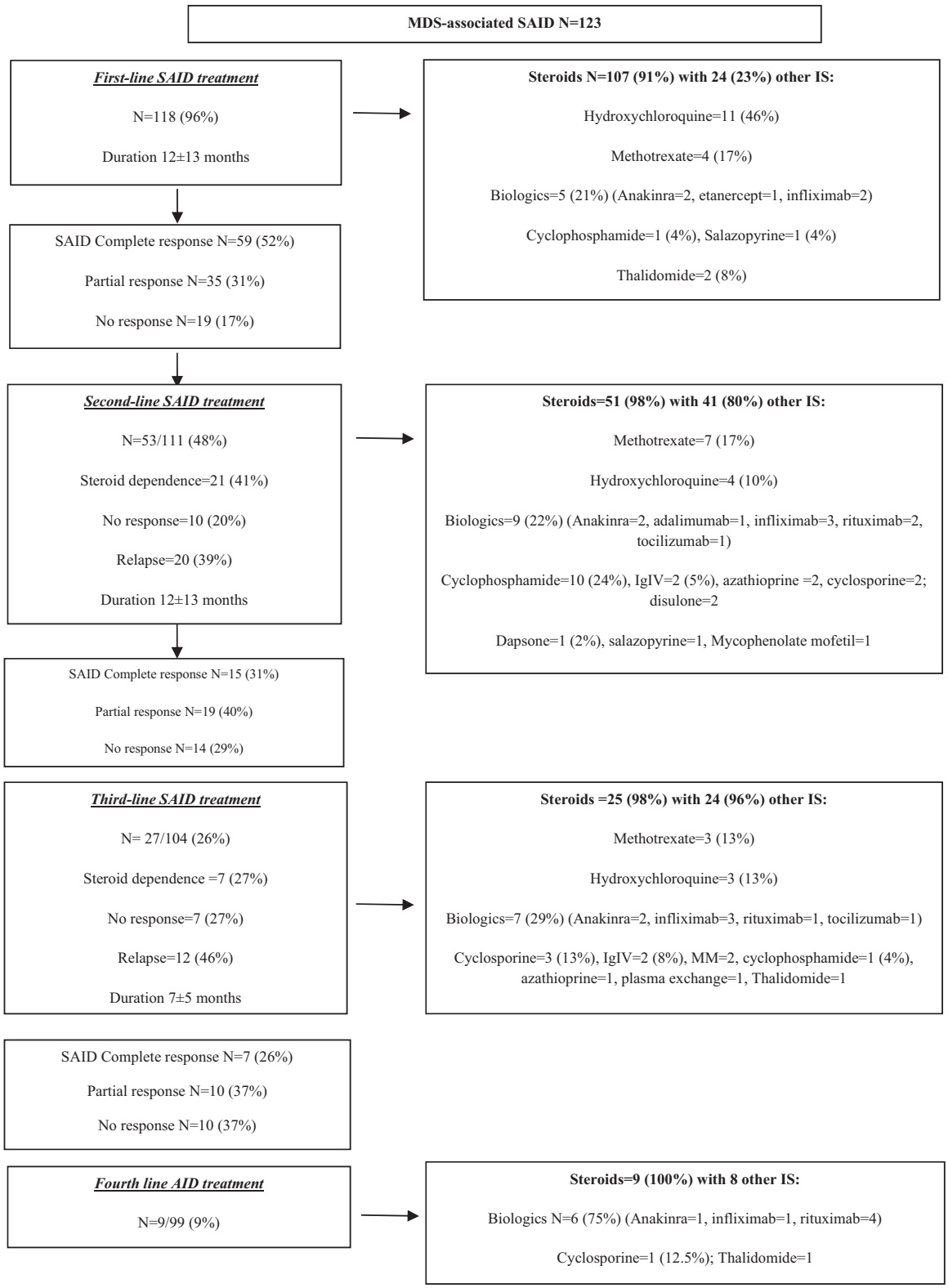
patients, including HCQ in 10% and various biologic targeted treatments in 22% (infliximab, adalimumab, anakinra, rituximab, tocilizumab) (Fig. 1). Despite the associated MDS/CMML, MTX and CYC were used in 17% and 24% of the cases, respectively. Complete or partial response to second-line treatment of SIAD was noted in 71% of the cases, but a third-line treatment was required in 60% of the evaluable patients due to non-response, steroid dependence or relapse (Fig. 1). Among treated patients who received biologic targeted treatments at any time ($n = 27$), a SIAD response (partial or complete) was noted in 9/20 (45%) patients.

Clinical manifestations and the number of involved organs, in particular skin, joint and eye involvement, improved during the follow-up (Table 4). CRP levels decreased during the follow-up but remained high at the last visit [42 mg/l (S.D. 67) *vs* 73 (72) at baseline; $P = 0.01$]. The daily amount of prednisone decreased during follow-up, from 41 mg/day (S.D. 21) to 17 (16) of prednisone equivalent at the last visit, with 32% of the patients having steroid dependence. Remission of the SIAD was achieved in 59% of patients, and 21% had steroid dependence. At least one severe infectious complication (requiring hospitalization and i.v. antibiotics) was noted in 41/61 cases (67%).

Relationship between outcome of MDS and *SIADs*

Among the 80 patients with MDS diagnosed before or concomitantly with SIADs who received SIAD treatment,

Fig. 1 Different lines of SIAD treatments and treatment responses



MDS: myelodysplastic syndrome; SIAD: systemic inflammatory and autoimmune disease.

TABLE 4 SIAD and MDS characteristics at baseline and during follow-up

Characteristic	Baseline (*n* = 123)	First visit (*n* = 77)	Second visit (*n* = 69)	Third visit (*n* = 69)	Four visit (*n* = 50)	Last visit (*n* = 109)
SIAD characteristics, *n* (%)						
Time from SIAD diagnosis, mean (S.D.), months		3.8 (2)	8 (3)	13 (14)	25 (9)	40 (31)
Fever	43 (35)	4 (6)	4 (7)	5 (9)	8 (20)	—
Skin	68 (55)	11 (17)	13 (22)	8 (14)	—	—
Joint	84 (70)	16 (24)	15 (25)	8 (14)	—	—
ENT	30 (27)	2 (3)	5 (8)	4 (7)	—	—
Peripheral neuropathy	14 (12)	6 (9)	7 (12)	4 (7)	—	—
Kidney	12 (10)	1 (2)	2 (3)	1 (2)	—	—
Lung	18 (17)	0	3 (5)	2 (4)	—	—
Eye	18 (16)	1 (2)	0	1 (2)	—	—
Number of organs, mean (S.D.)	2.6 (1.5)	0.7 (0.7)	1.2 (0.9)	1 (0.8)	—	—
ESR, mean (S.D.)	69 (52)	39 (37)	54 (52)	43 (31)	—	—
Fibrinogen, mean (S.D.), g/l	6 (3)	6 (8)	4 (2)	4 (2)	—	—
CRP, mean (S.D.), mg/l	73 (72)	18 (25)	24 (32)	26 (28)	28 (36)	42 (67)
SIAD treatments						
Steroids (prednisone), *n* (%)	107 (91)	55 (86)	49 (86)	49 (86)	33 (81)	73 (73)
Steroids, prednisone, mean (S.D.), mg/day	41 (21)	26 (18)	19 (16)	17 (15)	13 (11)	17 (16)
Steroid dependence, *n* (%)	—	—	14 (28)	15 (31)	10 (30)	23 (32)
Associated treatments, *n* (%)	24 (23)	16 (33)	18 (33)	24 (45)	11 (31)	30 (31)
SIAD remission, *n* (%)	—	35 (54)	26 (46)	25 (44)	20 (51)	61 (59)
MDS characteristics						
Haemoglobin, mean (S.D.), g/dl	10 (1.7)	10.8 (1.4)	10.5 (2)	10.5 (2)	10.3 (3)	9.8 (2)
Platelets, mean (S.D.), G/l	158 (104)	180 (94)	174 (122)	179 (117)	160 (111)	130 (90)
ANC, mean (S.D.), G/l	—	3654 (2652)	4354 (4772)	2936 (3062)	4102 (3684)	3674 (5929)
Stable MDS, *n* (%)	—	56 (86)	42 (74)	41 (73)	25 (64)	55 (57)
MDS progression, *n* (%)		9 (14)	15 (27)	15 (27)	14 (36)	42 (43)

MDS: myelodysplastic syndrome; SIAD: systemic inflammatory and autoimmune disease.

no significant increase in haemoglobin, ANC and platelet levels was seen after 6, 12 and 24 months and at the end of follow-up. The effect of MDS treatment on SIADs could be assessed in 20 patients where this treatment was concomitant with or started after SIAD diagnosis, including 11 patients treated with azacitidine, 5 by hydroxyurea, 3 by ciclosporin and 1 by low-dose cytarabine. SIAD response (complete/partial) was achieved in 15 patients (75%) after 3 months and 12 (56%) after 6 months, including in 9/11 (80%) and 6/11 (55%) for azacitidine, respectively. In patients treated with azacitidine, steroid amounts could be decreased from a mean of 44 mg/day (S.D. 19) at baseline to 22 (11) and 20 (19) at 3 and 12 months, respectively ($P = 0.06$ at 12 months).

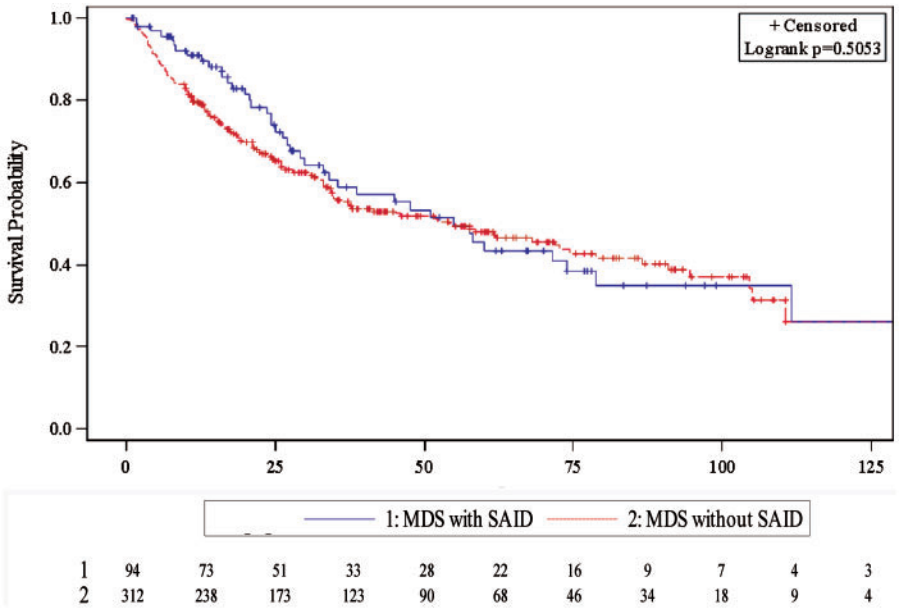
No relationship was found between response to first-line treatment of SIADs and response to first-line treatment of MDS. SIAD treatment response was independent of the time of MDS diagnosis, with 23 responses in 36 (64%), 23 in 37 (62%) and 10 in 23 (43%) patients with SIAD diagnosed before, concomitantly and after MDS, respectively ($P = 0.2$).

At 6, 12 and 24 months of follow-up from SIAD diagnosis, 22 (45%), 22 (49%) and 17 (55%) patients with stable MDS were also in SIAD remission ($P = 0.6$). Among patients with MDS progression, 11 (35%), 13 (62%) and 9 (53%) patients had active SIAD ($P = 0.5$). At last follow-up, among 60 patients with SIAD remission, 37 (62%) patients had stable MDS and 23 (38%) had MDS progression ($P = 0.3$) (supplementary Fig. S1, available at *Rheumatology* Online). Thus no obvious correlation was seen between SIAD activity and the outcome of MDS/CMML.

Survival

The median follow-up from MDS diagnosis was 25 months (IQR 12–58) in patients with MDS-associated SIAD and 25 months (IQR 12–46) in patients without MDS-associated SIAD ($P = 0.1$). Twenty-six (22%) and 83 (21%) patients with and without SIAD progressed to AML, respectively ($P = 0.7$) (Table 1). The median survival was 72 (IQR 59–105) and 75 (IQR 48–300) months in MDS/CMML with and without SIAD, respectively ($P = 0.2$) (Fig. 2). The 2- and 5-year overall survivals were 66% (95% CI 54, 75) and 52% (39, 62) in patients with MDS-associated SIAD *vs* 64% (95% CI 58, 70) and 55% (48, 62) in patients without MDS ($P = 0.5$). The percentage of censored data was 51% for the patients without SIAD and 55% for the patients with MDS-related SIAD, without a significant difference between the groups. Nineteen patients (4.7%) were lost during the follow-up, 3% among

Fig. 2 Overall survival in MDS patients with and without SIADs



MDS: myelodysplastic syndrome; SIADs: systemic inflammatory or autoimmune diseases.

patients without SIAD and 11% in patients with MDS-associated SIAD, and thus mainly follow-up duration could explain the number of censored cases. In multivariate analysis of patients with MDS and SIAD, higher IPSS [hazard ratio (HR) 3.1 (95% CI 1.6, 6)] and favourable karyotype [HR 0.3 (95% CI 0.2, 0.6)] were the only factors associated with overall survival.

After matching MDS patients with SIAD and MDS without SIAD based on IPSS and sex, MDS with SIAD patients less frequently had RAEB-1/2 and RARS and more frequently had CMML-1/2 subtypes, greater bone marrow blast percentage and poorer karyotype ($P < 0.05$) than MDS/CMML without SIAD patients. Overall survival in these matched patients remained similar in MDS with and without SIAD, with a median of 72 months (IQR 58–111) and 72 months (IQR 48–336), respectively ($P = 0.5$). Response to first-line treatment of SIAD was not significantly associated with overall survival [HR 1 (95% CI 0.5, 2)].

In patients with MDS/CMML and SIAD, no survival difference was noted based on the type of SIAD: the median survival was not reached for patients with vasculitis, 55 months (90% CI 30, 65) for patients with CTD, 58 months (90% CI 24, 336) for patients with rheumatological disease and 45 months (90% CI 10, 79) for patients with neutrophilic disease ($P = 0.3$).

Discussion

In this largest series of MDS/CMML associated with SIAD reported so far (to our knowledge), MDS/CMML associated with SIAD had worse baseline prognostic factors than MDS/CMML without SIAD, but with a similar overall survival. The underlying SIAD was variable and often did not fulfil complete diagnostic criteria. Finally, no clear correlation between the outcomes of SIAD and MDS was seen overall. The treatment of SIAD had a limited effect on MDS cytopenias, while treatment of MDS, especially with azacitidine, appeared to have an effect on signs of SIAD in the relatively small number of patients.

In our study, refractory cytopenia with multilineage dysplasia, RAEB-1 and CMML-1 were the most frequent WHO subtypes of MDS/CMML associated with SIAD, while RARS was underrepresented compared with MDS/CMML without SIAD. Previous smaller series of MDS/CMML associated with SIAD (of 13, 14, 20 and 46 patients with SIAD, respectively) tried to correlate the SIAD subtype with MDS subtype and found, in particular, RARS frequencies ranging from 0 to 14%, but no previous study had compared MDS with SIAD to a large control group of MDS without SIAD [2, 6, 8, 14–16]. CMML-associated SIAD has only been studied in a report of eight cases of CMML associated with PAN-like vasculitis [9]. In our study, only CMML-1 was found to be predominantly associated with a specific SIAD subtype, i.e. systemic vasculitis, and such an association with a specific WHO subtype had not been previously reported. In the literature, a total of 56 patients from five series of MDS/CMML and SIAD had available karyotypes, but no correlation between specific cytogenetic abnormalities and SIAD subtype has been made. In this large case series, the only correlation we found was between trisomy 8 and Behçet's disease, previously suggested by various case reports [17].

In our study, systemic vasculitis was the most frequent type of SIAD, followed by CTDs. In the literature, all types

of vasculitis have been described in association with MDS/CMML [2, 6, 8, 9, 16, 18]. A circumstantial association could be raised between MDS and GCA, especially because of the similar presentation age of the two conditions. However, GCA represented 23% of vasculitis in our work and was the most frequent vasculitis associated with MDS in another study [15]. Relapsing polychondritis was the most frequent CTD associated with MDS (58%) in our experience, confirming previous literature data, whereas only a few cases of SS or myositis in our work could raise a circumstantial association [2, 6, 8, 14–16].

In our study, 11% of patients had unclassified autoimmune and inflammatory features, and 19% did not fulfil complete classification criteria for SIAD, particularly for SLE and Behçet's disease. Even though it has been previously suggested that MDS/CMML-associated SIAD could be difficult to classify, this is the first work describing and classifying MDS/CMML-associated SIADs according to international diagnostic criteria and precisely assessing the frequency of unclassified SIAD [6]. This incomplete and non-specific clinical profile is in line with the underlying immunological abnormalities in our series, such as the high rate of atypical ANCA and non-specific ANAs [19].

Although MDS/CMML with SIAD had poorer baseline prognostic features, including higher bone marrow blast counts and poorer karyotype, the outcome, in terms of progression to AML and overall survival, was similar to that of MDS/CMML without SIAD included in the Groupe Francophone des Myélodysplasies registry. The outcome of patients with MDS/CMML-associated SIAD was variable in previously published literature [1, 5, 7, 8, 11, 12], and only two previous series of 13 and 46 MDS/CMML-associated SIAD patients compared with 57 and 189 non-matched MDS/CMML patients, respectively, showed no survival differences [6, 8]. In the present series we found similar outcomes in MDS/CMML with and without SIADs, and similar findings were seen when the patients with SIAD were matched to MDS without SIAD according to IPSS. In addition, in multivariate analysis, MDS characteristics (including WHO classification, karyotype and IPSS) remained the only prognostic factors of survival. Nevertheless, the insufficient follow-up duration could bias estimation of the survival difference between the two groups, as revealed by the number of censored data.

Treatment of MDS-associated SIAD is not codified. While experience with steroids has been previously reported, treatment strategies in steroid-dependent or refractory patients have not been described. In our experience, 83% of patients responded to first-line treatment, including 80% of those treated with steroids alone, but 50% of patients needed a second-line treatment regimen, mainly for steroid dependence or SIAD relapse. Steroid responsiveness in the present study was similar to that previously reported, but no data were previously available on the treatments in case of steroid dependence or in refractory patients. Because various SIADs were reported in our study, comparison of treatment response in SIADs without MDS may be difficult. In a previous study of patients with polyarteritis nodosa and microscopic polyangiitis without MDS, SIAD remission could be achieved with steroids alone in 82%, but 47% of patients subsequently required immunosuppressive drugs, and 44% were still on steroids at the end of follow-up [20]. By comparison, complete SIAD response was noted with steroids in 52% of our patients, steroid-sparing agents were used in 30% and 73% were on steroids at the last follow-up. The choice of steroid-sparing agents can be challenging in MDS/CMML-related SIAD, because they can worsen MDS-related cytopenias. At least one infectious complication occurred in 64% of our patients, but the specific impact of each immunosuppressive treatment could not be evaluated in our work. Biologic targeted treatments have been used in MDS for haematological purposes, even though their efficacy as single agents has been disappointing [21, 22]. A few case reports showed the efficacy of infliximab for MDS-associated SIAD, and 45% of SIAD patients had a response with biologic targeted treatment in our study, but without any effect on cytopenias of the underlying MDS [23]. In few case reports, SIAD treatment improved cytopenias of the underlying MDS, but in previous large reports there was no haematological response to immunosuppressive therapy [8, 16], and similar data were found in our study.

In contrast, MDS treatment, in particular azacitidine, had an effect on SIADs in 9/11 (80%) and 6/11 (55%) treated patients after 3 and 6 months, respectively, with a decrease of the steroid dose and the number of steroid-dependent patients. The efficacy of hypomethylating agents on refractory MDS-related SIAD had been previously suggested in only a few case reports [24, 25]. Prospective studies are clearly needed to confirm the efficacy of hypomethylating agents on outcome in MDS/CMML-related SIADs. Finally, no close correlation could be found between the outcome of MDS and SIADs over time; in particular, 38% of patients with remission of SIADs had MDS progression at the last follow-up.

In conclusion, MDS-associated SIADs have variable and often incomplete features, rendering them difficult to classify. Compared with MDS without SIADs, they are characterized by more unfavourable baseline characteristics, but with a similar survival. Treatment of SIADs, especially with steroids, generally proved effective, but with a high incidence of steroid dependence and relapse. On the other hand, treatments of MDS, especially azacitidine, may lead to improvement of SIADs, although larger and prospective studies are needed to confirm our preliminary findings.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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