Inflammatory Arthritis in Patients With Myelodysplastic Syndromes

A Multicenter Retrospective Study and Literature Review of 68 Cases

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Abstract: We describe the characteristics and outcome of inflammatory arthritis in patients with myelodysplastic syndrome (MDS) in a French multicenter retrospective study.

Twenty-two patients with MDS (median age, 77.5 yr [interquartile range, 69–81]; 10 women) were included. Inflammatory arthritis presented as polyarthritis in 17 cases (77%) and with symmetric involvement in 15 cases (68%). At diagnosis, the median disease activity score 28 based on C-reactive protein (DAS28-CRP) was 4.5 [2–6.5]. Two patients had anti-citrullinated protein antibodies (ACPAs), and 1 had radiologic erosions. The median time between the diagnoses of arthritis and MDS was 10 months [6–42], with a median articular symptom duration of 3 months [2–8]. The diagnosis of both diseases was concomitant in 6 cases (27%); arthritis preceded MDS in 12 cases (55%), and occurred after MDS in 4 (18%). While the number of swollen and tender joints significantly decreased during follow-up, as did the median DAS28-CRP (from 4.3 [3.8–4.6] at baseline to 2.9 [1.75–3.3]; $p < 0.05$), CRP remained elevated (CRP >20 mg/L) in 8 patients (42%). Nevertheless, radiographic progression and new ACPA positivity were not observed during a median follow-up of 29 months [9–76]. While most of the patients were treated with steroids (n = 16) for arthritis, additional treatment was administered in only 4 patients (hydroxychloroquine, n = 2; sulfasalazine [Salazopyrin] and etanercept, n = 1, respectively). Eleven patients died during follow-up from acute myeloid leukemia (n = 5); infections (n = 3); or cerebral bleeding, cardiorespiratory failure, or undetermined cause (n = 1, respectively).

Inflammatory arthritis associated with MDS can have various presentations and is often seronegative and nonerosive. Steroids alone are the most common treatment in MDS-associated arthritis, but that treatment is insufficient to control arthritis. Steroid-sparing strategies need to be identified.

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Abbreviations: ACPA = anti-citrullinated protein antibody, ACR = American College of Rheumatology, AML = acute myeloid leukemia, ANA = antinuclear antibodies, CMML = chronic myelomonocytic leukemia, CRP = C-reactive protein, DAS28-CRP = disease activity score 28 based on C-reactive protein, ESR = erythrocyte sedimentation rate, IPSS = International Prognostic Scoring System, MDS = myelodysplastic syndrome, MDS-U = unclassified MDS, RAEB1 = refractory anemia with excess blasts-1, RAEB2 = refractory anemia with excess blasts-2, RARS = refractory anemia with ring sideroblasts, RCMD = refractory cytopenia with multilineage dysplasia, RCUD = refractory cytopenia with unilineage dysplasia, RS3PE = remitting seronegative symmetrical synovitis with pitting edema, WHO = World Health Organization.

INTRODUCTION

Myelodysplastic syndromes (MDSs) are clonal marrow stem cell disorders characterized by ineffective hematopoiesis resulting in cytopenia and a high risk of progression to acute myeloid leukemia (AML). MDSs are frequently associated with various autoimmune and systemic features, but the mechanisms of this association remain insufficiently understood.[19] The association with inflammatory arthritis, including rheumatoid or undifferentiated arthritis, polymyalgia rheumatica, and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, has primarily been described in case reports and small series.[6,12,15,20,34] Information is still lacking regarding the evolution of the disorders as well as the use of and response to specific treatments for MDS-associated arthritis.

In this French multicenter, retrospective study, we described the characteristics of MDS-associated inflammatory arthritis

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TABLE 1. Baseline Characteristics and Follow-Up of Patients in the French Study

Characteristics	Number of Patients Available for Evaluation				
	Baseline Assessment (n = 22)	First Visit (n = 19)	Second Visit (n = 11)	Third Visit (n = 9)	Last Visit (n = 19)
Arthritis characteristics					
Delay from the diagnosis (mo)	—	6 [3–14]	14 [8–32]	19 [13–27]	38 [17–61]
Arthralgia	22 (100%)	13 (68%)**	6 (55%)**	3 (33%)**	9 (47%)**
Arthritis	16 (73%)	5 (26%)**	2 (18%)**	1 (11%)**	3 (16%)**
Number of tender joints	6 [4–8]	2 [0–4]**	4 [0–4]*	0 [0–3]**	0 [0–4.5]**
Number of swollen joints	3 [0–4.5]	0 [0–2]**	0 [0–1]*	0 [0]*	0 [0]**
Morning stiffness (hr)	1 [0–1]	0 [0–0.5]**	0 [0–0.5]**	0 [0–0.5]*	0 [0]**
Erosions	1 (5%)	1 (5%)	—	—	1 (5%)
CRP (mg/L)	30 [10–58]	10 [5–30]*	25 [3.5–56]	25 [8–140]	10 [3.5–55]
CRP >20 mg/L	14 (64%)	7 (37%)	5 (45%)	4 (44%)	8 (42%)
DAS28-CRP	4.3 [3.8–4.6]	3 [1.8–3.7]**	2.7 [2.2–4]*	2.8 [1.6–3.3]**	2.9 [1.75–3.3]**
Efficacy (by physician)		15 (79%)	7 (64%)	6 (67%)	15 (79%)
Arthritis treatments					
Steroids (prednisone)	16 (73%)	12 (63%)	10 (91%)	8 (89%)	14 (74%)
Steroids (prednisone; mg/d)	27.5 [16–35]	15 [10–25]	10 [9.5–20]	9.5 [5–17]*	8 [5–15]**
Steroid dependence	—	5 (26%)	4 (36%)	1 (11%)	2 (11%)
Other treatments	4 (18%) Hydroxychloroquine (n = 2) Etanercept Salazopyrin	4 (21%) Hydroxychloroquine (n = 2) Etanercept Salazopyrin	3 (27%) Hydroxychloroquine (n = 2) Salazopyrin	2 (22%) Hydroxychloroquine	4 (21%) Hydroxychloroquine (n = 3) Anakinra
MDS characteristics					
Hemoglobin (g/dL)	9 [8–11]	11 [8.5–11.5]	11 [8.7–13]	10 [8–11]	10 [8–12]
Platelets (n/mm^3)	163 [62–657]	114 [50–242]	233 [75–250]	150 [40–244]	75 [12–146]*
Neutrophils (n/mm^3)	2600 [740–5070]	1500 [1000–3000]	1300 [1150–2500]	1200 [1000–3105]	2300 [1000–4550]
Blasts (%)	0 [0–8]	0 [2]	0 [0–0]	0 [0–2.5]	0 [0–1]
MDS progression	—	3 (16%)	2 (18%)	4 (44%)	4 (21%)
MDS treatment	4 (18%)	6 (32%)	3 (27%)	3 (33%)	6 (32%)

Values are medians (interquartile ranges) and numbers (frequencies).

*$p < 0.05$ versus baseline.

**$p < 0.005$ versus baseline.

as well as the outcome and specific treatments. A literature review of MDS-associated arthritis was also performed.

PATIENTS AND METHODS

Patient Selection

Data were collected retrospectively from the physicians in charge of the patients. The physicians were asked to complete a standardized questionnaire distributed online with the support of the Club Rhumatismes et Inflammation (available online at http://www.cri-net.com) and the National Society of Internal Medicine (SNFMI) (see Supplemental Digital Content, http://links.lww.com/MD/A25, English version of the questionnaire). The inclusion criteria were as follows: 1) MDS according to the 2008 World Health Organization (WHO) criteria;[47] 2) >2 tender joints and/or swollen joints for >6 weeks, with a diagnosis of inflammatory arthritis; 3) absence of extraarticular systemic features; 4) time between arthritis and MDS diagnosis <5 years. The exclusion criteria included crystal and septic arthritis. The study was performed in accordance with the ethical standards of the Helsinki Declaration.

Data Collection

One physician (AM) used the predefined standardized form to collect patient data. Patient clinical, laboratory, and radiologic data as well as treatments were recorded at baseline, at different points during the follow-up, and at the last visit (Table 1). The evaluated joints included the metacarpophalangeal (×10) and proximal interphalangeal (×10) joints, wrists (×2), metatarsophalangeal joint (×10), shoulders (×2), knees (×2), ankles and elbows (×4). Laboratory data included standard tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum

fibrinogen, serum gammaglobulins, CH50, C3, C4, rheumatoid factor, anti-citrullinated protein antibodies (ACPAs), and antinuclear antibodies (ANAs) if available.

Definitions

The 1987 and 2010 American College of Rheumatology (ACR) criteria for rheumatoid arthritis were retrospectively applied to all patients.[2,4] The response to treatment of arthritis was assessed using a subjective physician assessment and according to the DAS28-CRP variation (except for patients with polymyalgia rheumatica). Steroid dependence was defined as a daily prednisone dose ≥20 mg.

MDS was classified according to the 2008 WHO criteria.[47] The International Prognostic Scoring System (IPSS) was retrospectively assessed, including the extent of cytopenia, cytogenetics, and the percentage of blasts in the bone marrow.[14,23] The response of MDS to treatment was retrospectively defined according to the 2006 International Working Group criteria.[14]

Statistical Analysis

Descriptive statistics included the medians (interquartile ranges [IQRs]) as appropriate for continuous variables and frequencies (percentages) for categorical variables. To consider missing data in the analyses, the results were expressed comparatively to the total number of available data. The Fisher exact test was used to compare categorical variables, and the nonparametric Mann-Whitney test or Wilcoxon test was used to compare continuous variables. A p value < 0.05 was considered significant. Statistical analyses were performed using Prism software (GraphPad Software, San Diego, CA).

Literature Review

Search Strategy

A literature search was performed by 2 investigators (AM and OF) using MEDLINE (National Library of Medicine, Bethesda, MD) (searching records from January 1987 to October 2012) using the following keywords: myelodysplastic syndrome, arthritis, rheumatoid arthritis, undifferentiated arthritis, systemic diseases, auto-immune diseases, polymyalgia rheumatica, and RS3PE. All articles with sufficient data were included in the literature review. The literature search yielded 31 citations; 23 were analyzed and included in the present study (7 were excluded because of insufficient data concerning arthritis, and 1 paper was in Japanese).[6–13,15–17,19–22,24–32,34–43,46] Among these 31 studies, only 5 included more than 3 patients, with the largest study including 6 described cases (see Tables 2–4).

RESULTS

Baseline Patient Characteristics

Twenty-two patients with MDS and arthritis (median age, 77.5 yr [IQR, 69–81]; 12 men, 10 women) were included. The diagnosis of MDS included refractory cytopenia with unilineage dysplasia (RCUD) (n = 1), refractory anemia with ring sideroblasts (RARS) (n = 1), refractory anemia with excess blasts-1 (RAEB1) (n = 5), refractory anemia with excess blasts-2 (RAEB2) (n = 3), refractory cytopenia with multilineage dysplasia (RCMD)(n = 8), MDS with 5q deletion (n = 2), chronic myelomonocytic leukemia (CMML) (n = 1), and unclassified (MDS-U) (n = 1).) Cytogenetics were available in 15 patients and were favorable in 11 cases including normal karyotype in 5/15 cases (33%), intermediate and poor in 2 cases each. The IPSS was low (n = 3), intermediate-1 (n = 7), and intermediate-2 (n = 5). The median medullar blast count was 4.5 [0–15], with a normal karyotype in 5/15 cases (33%).

Inflammatory arthritis presented as polyarthritis in 17 cases (77%) and with symmetric involvement in 15 cases (68%). Four patients had isolated shoulder arthralgia, compatible with polymyalgia rheumatica, and 4 (18%) had bilateral pitting edema of the hands with polyarthritis consistent with RS3PE syndrome. At diagnosis, rheumatoid factor was present in 5 patients (23%), and 2 of the 5 had ACPAs (9%), with radiologic erosions in 1 case. The median numbers of ACR-1987 and ACR-2010 rheumatoid arthritis criteria present were 3 [2.5–4] and 5 [4–7], respectively, with 8/18 patients (44%) and 6/18 (33%) fulfilling the rheumatoid arthritis criteria, respectively. The 2 sets of rheumatoid arthritis criteria were significantly correlated, with a kappa of 0.6 ($p < 0.05$).

The median time between the diagnoses of arthritis and MDS was 10 months [6–42], with an articular symptom duration of 3 months [2–8]. The appearance of these 2 diseases was concomitant in 6 cases (27%); arthritis preceded MDS in 12 cases (55%) and occurred after MDS in 4 (18%).

Outcome

The treatments administered during the follow-up and evolution of arthritis and MDS are shown in Table 1. While the number of swollen and tender joints and the median DAS28-CRP significantly decreased during follow-up (from 4.3 [3.8–4.6] at baseline to 2.9 [1.75–3.3]; $p < 0.05$), CRP remained elevated (CRP >20 mg/L in 8 [42%] vs. 14 patients at baseline). Nevertheless, no patients showed any radiographic progression or new ACPA positivity during a follow-up period of 29 months [9–76]. No significant correlation was found between MDS

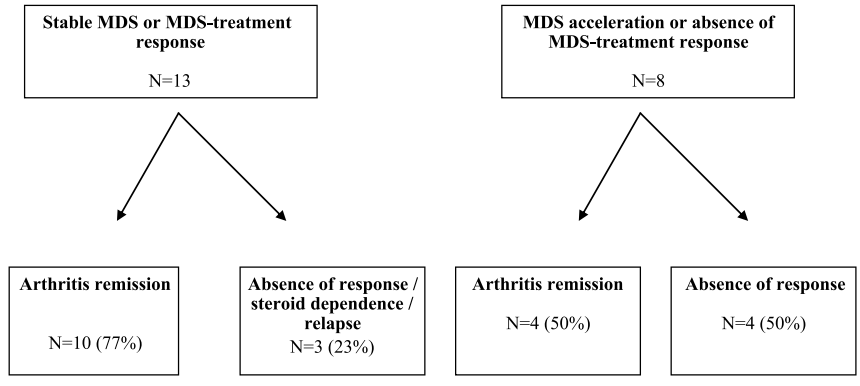

FIGURE 1. Inflammatory arthritis outcome in relation to MDS evolution (data available for 21 of 22 patients).

TABLE 2. Rheumatoid Arthritis and Undifferentiated Arthritis Associated With MDS, Previous Reports

First Author Year	Age/Sex (yr)	Time Relation Arthritis-MDS (mo)	Type of MDS	Type of Arthritis	ESR/CRP (mm/h)/ (mg/L)	RF	Erosion	ACR-1987 RA	Treatment	Treatment of MDS	MDS Outcome	Follow-Up (mo)	Arthritis Outcome
Castro 1991[12]	74/M	-48	RAEB1-2	P	107/	+	None	Yes	Prednisone				Remission
George 1992[20]	NA	+18	RC	P	84/	−	None	Yes	Prednisone		Aggravation		Remission
George 1992	NA	−9	RAEB2	P	110/	−	None	Yes	NSAID		AL		Remission
George 1992	NA	Concomitant	RARS	P	33/	−	None	Yes	NSAID		Aggravation		Relapse
George 1992	NA	+5	RAEB1	O		−	None	None	NSAID		Aggravation		Remission
George 1992	NA	−13	RAEB2	P	64/	−	None	Yes	HC, prednisone		Aggravation		Steroid dependence
George 1992	NA	Concomitant	RAEB1	P	60/	−	None	Yes	Prednisone				Recurrence
Pajus 1992[42]	74/F	−6	CMML	P		+	None	Yes	Prednisone	None	AL	24	Remission
Pajus 1992	54/M	+12	CMML	O		−	None	None	Prednisone 30 mg/d				Steroid dependence
Pajus 1992	75/M	−5	RAEB2	O		−	None	None	None	Aracytine	Stable	36	Remission
Pajus 1992	58/F	+24	5q-	M	35/	−	None	None	None	None	Stable	36	Remission
Kuzmich 1994[32]	64/M	−9	RCMD	P	52/	−	None	Yes	HC, Prednisone	Transfusions	AL	18	Remission
Kuzmich 1994	61/M	+5		P	55/	−	None	None	NSAID			18	No response
Pando 1995[43]	59/M	+2	RAEB1-2	O	68/		None	None	Prednisone 30 mg/d	None	AL	6	No response
Chandran 1996[13]	80/M	+36	RC	P	85/5	−	None	Yes	Prednisolone 15 mg/d	Transfusion	Stable	6	Remission
Chandran 1996	84/F	−6	RARS	P	71/1	−	Yes	Yes	NSAID	None			No response
Chandran 1996	75/M	+9	CMML	P	10/14	−	None	Yes	Prednisolone			11	Remission
Chandran 1996	73/M	−3	CMML	P	70/20	−	None	None	Prednisolone 20 mg/d		AL	12	Remission
Carvajal 1996[11]	72/M	+24	RAEB1-2	P	72/	+	None	Yes	Prednisone	Transfusions		12	Steroid dependence
Carvajal 1996	70/F	Concomitant	CMML	P	127/	−	None	None	Prednisone		AL	10	Steroid dependence
Kaufman 1997[29]	77/F	Concomitant	RAEB1-2	O	121/	−	None	None	Methylprednisolone 40 mg/d	VP16	AL	9	Remission/ relapses
Cuende 1999[15]	48/M	+3	RAEB1-2	P	110/193	−	None	None	Prednisone 1 mg/kg per d	Transfusions	Stable	6	Remission
Nam 1999[38]	31/F	+24	RCMD	P		+	Yes	None	Prednisone, HC	Androgens, transfusions		5	No response
Soubrier 2002[46]	77/M	−12	RAEB1	P	93/42	+	None	Yes	Prednisone 10 mg/d, HC	Aracytine	AL	7	No response

Bouali 2005[10]	53/M	Concomitant	RCMD	P-		+	None	Yes				
Bouali 2005	67/F	−4	RARS	P		−	None	NA				
Giagounidis 2005[21]	63/F	−48	5q-	P		−	None	NA	Prednisone 10 mg/d	Aracytine	Stable	21	No response
Nozaki 2008[39]	57/F	−1	RC	P	140/116	+	None	Yes	Prednisone 10 mg/d, tacrolimus	None	Stable	6	Remission

Abbreviations: ACR-1987 RA = American College of Rheumatology 1987 rheumatoid arthritis criteria, AL = acute leukemia, HC = hydroxychloroquine, M = monoarthritis, NA = not available, NSAID = nonsteroidal antiinflammatory drugs, O = oligoarthritis, P = polyarthritis, RA = rheumatoid arthritis, RF = rheumatoid factor.

evolution and inflammatory arthritis, although among patients with stable MDS or responders to MDS treatment, 10 patients (77%) experienced arthritis remission compared to 4 (50%) in patients with progressive disease (Figure 1) ($p = 0.2$). The arthritis treatments included steroids in 16/22 patients; only 4 patients received other treatments (hydroxychloroquine, n = 2; sulfasalazine [Salazopyrin] and etanercept, n = 1, respectively). For MDS, 6 patients received potentially disease-modifying drugs, including azacitidine in 4 cases and lenalidomide in 2, while other treatments included androgens (n = 1), cyclosporine (n = 1), and erythropoietin (n = 8) for cytopenias. Among 4 patients receiving azacitidine, articular symptoms improved in 2 patients, with 1 patient achieving hematologic improvement and 1 patient stable while on azacitidine. No patient receiving lenalidomide improved in respect to articular symptoms. Complications that could be related to MDS and/or steroids were noted in 11 cases: infections (n = 4), osteoporosis and fractures (n = 2), steroid-related myopathy (n = 2), cardiovascular failure (n = 2), and secondary hemochromatosis (n = 3). Eleven patients (50%) died during follow-up as a result of AML (n = 5), infections (n = 3), cerebral bleeding, cardiorespiratory failure or undetermined cause (n = 1, respectively).

Literature Review

Rheumatoid Arthritis or Undifferentiated Arthritis

For the literature review we analyzed 42 cases with rheumatoid or undifferentiated arthritis, including 14 cases from the current study (Table 2). Arthritis was typically polyarticular (n = 34; 83%) and symmetrical (80%) with rheumatoid factor in 12/40 cases (30%), and radiologic erosions were present in only 2 cases (5%). The median time between the diagnosis of arthritis and MDS was 9 months [3.5–24]; arthritis preceded MDS in 21 cases (50%), and the 2 diseases were concomitant in 5 cases (12%). The number of ACR-1987 rheumatoid arthritis criteria met was 4 [2.5–4], and ≥4 were met in 21/41 patients (51%). Corticosteroids were used in 29/41 cases (71%), with daily prednisone at 30 mg [15–35]. Another disease-modifying antirheumatic drug was used in only 8 cases: hydroxychloroquine (n = 5) and etanercept, tacrolimus, and sulfasalazine (Salazopyrin) (n = 1, respectively). The types of MDS were RCUD (n = 4), RAEB-1/-2 (n = 15), RARS (n = 3), MDS with 5q deletion (n = 4), CMML (n = 6), and RCMD (n = 8). With a median follow-up of 12 months [8–33], 15/28 (54%) of the MDS patients had received treatment, including low-dose cytarabine, (n = 3), azacitidine (n = 2), androgens (n = 2), VP16 (n = 1), cyclosporine (n = 1), and erythropoietin (n = 5). MDS progression occurred in 10/23 cases (43%), with death in 11/19 cases (58%), whereas uncontrolled arthritis persisted in 17/34 cases (50%), with steroid dependence in 25%.

Polymyalgia Rheumatica

Eighteen cases of polymyalgia rheumatica, including our 4 cases, were analyzed (Table 3). Giant cell arteritis was reported in 3 cases (17%). The median time between the diagnosis of polymyalgia rheumatica and MDS was 4 months [3–27]; arthritis preceded MDS in 10 cases (56%), and the 2 diseases were concomitant in 3 cases (17%). Prednisone was used in all cases, with a median daily dose of 20 mg [19–40]. Additional treatment was administered in 3 cases (methotrexate in 2 cases and hydroxychloroquine in 1 case). Specific MDS treatment was administered in 6/16 cases: erythropoietin (n = 4) and azacitidine, lenalidomide, and androgens (n = 1, respectively). MDS progression occurred in 5/17 cases. Over a median follow-up of 29 months [10–47], polymyalgia rheumatica was in

TABLE 3. Polymyalgia Rheumatica Associated With MDS, Present and Previous Reports

First Author Year [ref]	Age/Sex (yr)	Time Relation Arthritis-MDS (mo)	GCA	ESR (mm/h)	CRP (mg/L)	Type of MDS	IPSS	Prednisone (mg/d)	MDS Treatment	MDS Outcome	Follow-Up (mo)	PMR Outcome
Kalra 1987[28]	72/F	Concomitant	N	114	NA	RAEB2	NA	15	None	Progression	6	Remission
Kohli 1994[30]	83/F	4	N	98	NA	RC	NA	20	Transfusions	Stable	5	Steroid dependence
Kohli 1994	59/F	4	N	105	NA	5q-	NA	15	Transfusions	Stable	60	Steroid dependence/relapses, methotrexate
Kohli 1994	67/F	3	Y	68	NA	RC	NA	60	Transfusions	Stable	228	Steroid dependence/relapses
Kuzmich 1994[32]	82/F	−12	N	54	NA	RAEB2	NA	15	None	Progression	24	Remission/relapses
Mok 1996[36]	59/F	Concomitant	N	140	NA	RAEB1	1	20	Transfusions	Stable	19	Remission
Billstrom 1995[9]	68/F	−4	Y?	105	NA	RAEB2	3.5	20			4	Remission
Hubscher 1996[27]	80/M	−4	N	140	NA	RAEB2	2.5	40	Androgens	Progression	8	Steroid dependence
Hubscher 1996	83/M	−4	N	130	NA	RC	1	40	None	Progression	9	Steroid dependence
Berthelot 1997[6]	82/F	+96	N	50	40	RAEB1	0	15	Transfusions	Stable	36	Remission
Berthelot 1997	71/M	−32	N	110	70	RCMD	0.5	30	Transfusions	Stable	47	Relapses/ hydroxychloroquine
Berthelot 1997	65/M	−10	N	60	46	RCMD	NA	51	NA	Stable	32	Steroid dependence/relapses
Giannouli 2004[22]	67/M	−5	Y	NA	NA	RARS	2	NA	Erythropoietin, transfusions	Stable	14	Remission
Giannouli 2004	69/F	Concomitant	N	NA	NA	RAEB1	NA	NA	Erythropoietin, transfusions	Stable	47	Remission/methotrexate
PR, PMR Case 1	77/M	−2	N	100	120	RCMD	0.5	60	Erythropoietin/ lenalidomide	No response	31	Steroid dependence
PR, PMR Case 2	80/M	+50	N	60	20	RAEB2	1.5	20	Azacytidine	No response	72	Partial response
PR, PMR Case 3	84/F	−34	N	15	27	RARS	NA	35	Erythropoietin	Progression	58	Remission/relapses
PR, PMR Case 4	74/F	−32	N	NA	NA	RCMD	1	30	None	Stable	27	Steroid dependence

Abbreviations: See previous tables. GCA= giant cell arteritis, HR = hematologic response, N = none, NA = not available, PMR = polymyalgia rheumatica, PR = present report, RC = refractory cytopenia.

TABLE 4. RS3PE Associated With MDS, Present and Previous Reports

First Author Year	Age/Sex (yr)	Time Relation Arthritis-MDS	Type of MDS	ESR (mm/h)	CRP (mg/L)	RF	ACPA	Erosion	Prednisone (mg/d)	Other	MDS Treatment	MDS Outcome	Follow-Up (mo)	Arthritis Outcome
Hernandez-Beriain 1996[26]	88/M	+2	RC	58	NA	Negative	NA	None	15	None	None	Stable	8	Remission
Manganelli 2001[34]	72/M	Concomitant	RAEB1	100	52	Negative	NA	None	20	None	Transfusions	Stable	31	Remission/ relapse
Beyne-Rauzy 2001[8]	72/M	Before MDS	RAEB1-2	NA	NA	Negative	Negative	None	20	None	NA	NA	NA	No remission
Paira 2002[41]	75/M	+11	NA	60	NA	Negative	NA	None	12	None	Erythropoietin, androgens	NA	NA	No remission/ steroid dependence
PR, RS3PE Case 1	81/M	Concomitant	RAEB1	NA	115	Negative	Negative	None	10	None	Azacytidine	NA	2	
PR, RS3PE Case 2	77/M	−36	RAEB2	80	50	Negative	Negative	None	20	None	Lenalidomide	Stable	74	Remission
PR, RS3PE Case 3	51/F	−2	RAEB1	10	5	Negative	Negative	None	0	None	Azacytidine	AL	24	Remission
PR, RS3PE Case 4	89/M	−6	RCMD	65	50	Negative	Negative	None	10	HC	Erythropoietin	Stable	20	Remission

Abbreviations: See previous tables.

remission in 7/18 cases (39%), and 8/18 cases (44%) had steroid dependence.

RS3PE Syndrome

Eight cases of RS3PE, including our 4 cases, were analyzed (Table 4). No patient presented with rheumatoid factor or radiologic erosion. Corticosteroids were used in all patients, with a daily dose of 14 mg [10–20], and additional hydroxychloroquine treatment in 1 case. MDS was treated in 5/7 cases: erythropoietin (n = 2) and androgens, azacitidine, and lenalidomide (n = 1, respectively). MDS progression was observed in 1/5 cases. Over a median follow-up of 22 months [11–30], arthritis remission was achieved in 4/7 cases (57%), and steroid dependence was reported in 2/7 cases (29%).

All Patients With MDS Arthritis

Among 68 patients with MDS-associated arthritis, the median follow-up was 20 months [8–36]. The median time between the diagnosis of arthritis and MDS was 5 months [1–24]; arthritis preceded MDS in 34 cases (50%), and the 2 diseases were concomitant in 9 cases (13%) (Figure 2). Additionally, 12/49 (24%) patients were positive for rheumatoid factor, and 3/51 (6%) exhibited radiologic erosions. MDS-associated arthritis fulfilled the ACR-1987 rheumatoid arthritis criteria in 21 cases (31%), presented as polymyalgia rheumatica in 18 cases (26%), RS3PE syndrome in 8 cases (12%), and undifferentiated arthritis in 21 cases (31%). As shown in Table 5, MDS and arthritis appeared less than 12 months apart in most patients with RS3PE, polymyalgia rheumatica, and undifferentiated arthritis, and in 57% of patients with RA. Steroids were used in 54 cases (78%) with a median daily dose of 20 mg [15–35] of prednisone. Complete arthritis remission was achieved in 22/65 cases (34%). The majority of patients had RAEB-1/−2 (n = 23/66; 35%). MDS was treated in 24/40 cases (60%), with stable disease in 26/57 cases (46%) and disease progression in 16/44 cases (36%).

DISCUSSION

In the current study focusing on MDS-associated arthritis, we describe 4 rheumatologic patterns of MDS-associated arthritis: rheumatoid and undifferentiated arthritis, polymyalgia rheumatica, and RS3PE syndrome. Despite the frequent and persistent increase of acute-phase reactants, radiologic erosions

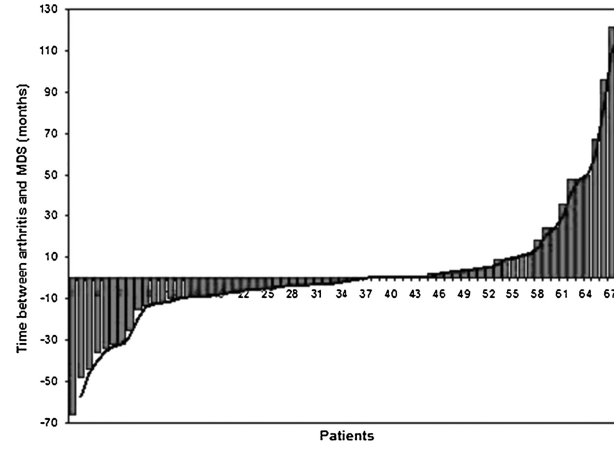

FIGURE 2. Time between arthritis and MDS diagnoses in all patients.

TABLE 5. Delay Between Arthritis and MDS

Arthritis-MDS Delay	N Patients	RS3PE Patients	Polymyalgia Rheumatica Patients	RA Patients	Undifferentiated Arthritis Patients
≤12 mo	47 (69%)	7 (88%)	13 (72%)	12 (57%)	15 (71%)
<24 mo	54 (80%)	0	0	5	2
<36 mo	59 (87%)	1	3	1	0
<48 mo	61 (90%)	0	0	1	1
>48 mo	7	0	2	2	3
Total	**68**	**8**	**18**	**21**	**21**

Abbreviations: See previous tables.

appeared to be rare, in contrast to isolated rheumatoid arthritis. Specific rheumatoid arthritis treatments for MDS-associated arthritis and steroid-sparing agents were rarely used. MDS-associated arthritis appears to be more frequent in RAEB, and uncontrolled arthritis may evolve in parallel with the underlying MDS.

The current study confirms and expands on the previous case reports and series of MDS-associated arthritis.[6–13,15–17,19–22,24–32,34–43,46] In particular, no specific rheumatologic features suggested MDS-associated arthritis, and despite polyarticular symmetrical arthritis and frequent inflammatory syndrome, the presence of rheumatoid factor was relatively rare. The presence of rheumatoid arthritis was frequent, but MDS-associated arthritis also appeared as polymyalgia rheumatica or RS3PE syndrome and remained undifferentiated arthritis in 32% of cases. The concomitant appearance of these features in less than 12 months in most of the patients highlights the link between these 2 diseases. A fortuitous association may have been present in particular for rheumatoid arthritis cases with more than 4 years' delay. Radiologic destruction appears to be exceptional. Uncontrolled arthritis and steroid dependence were observed in as many as 50% and 30% of patients, respectively.

MDS-associated arthritis frequently precedes MDS, and the possibility of inflammatory anemia could lead to the misdiagnosis of associated MDS. The persistence of anemia despite the remission of arthritis, associated cytopenia, and the importance of the increase of acute-phase reactants could indicate MDS. In patients with polymyalgia rheumatica, as described in the current study and the literature review, a poor response to steroids or steroid dependence should suggest the presence of associated MDS, particularly if cytopenia is observed.

The presence of systemic manifestations did not appear to affect the MDS prognosis, except in patients with vasculitis and cryoglobulinemia.[16] The prognosis of MDS-associated arthritis may be less severe than the prognosis of MDS-associated vasculitis. However, similar to MDS vasculitis, MDS-associated arthritis is better controlled when the treatment of MDS is efficient.[18] Compared to non-MDS rheumatoid arthritis, the use of disease-modifying antirheumatic drugs and steroid-sparing agents is very rare and could most likely explain the poor response and high steroid dependence (20%–40%). Nevertheless, the importance of steroid complications in patients with underlying hematologic immunodeficiency, as noted in our study, highlights the significance of steroid-sparing strategies.

The mechanisms of autoimmune disorders associated with MDS remain poorly understood. The presence of immune dysregulation in MDS, as characterized by an impaired CD8 response and an imbalance of T-regulatory cells and Th-17 cells could also explain the emergence of autoimmune disorders.[1] Cytokine targeting, particularly TNFα antagonists, is alone insufficient for MDS treatment, but some reports have sparked interest for their use in MDS-associated autoimmune disorders.[5,45] Recently, hypomethylating agents, such as azacitidine and decitabine, have been shown to treat MDS effectively, and several reports have shown the benefits of these agents in MDS-associated autoimmune disorders.[3,44] Similarly, lenalidomide has been shown to have immunomodulatory action in malignancy and to induce an increase in T-regulatory cells and a Th-17 cell imbalance; it may also be effective for the treatment of autoimmune features.[33] In the current study, arthritis appeared to be better controlled in patients with stable MDS or treatment response. Nevertheless, large studies lack information on the impact of such treatments on MDS-associated autoimmune disorders, which is required to determine the optimal strategy in this setting.

Some limitations should be mentioned, including the retrospective design, the amount of missing data, and the small number of patients in the current study. The impact of MDS treatment on arthritis activity was difficult to assess, as treatments have changed over the years, and in particular, the impact of hypomethylating agents on arthritis could not be evaluated due to the small number of patients treated. Additionally, the efficacy of other immunosuppressive and steroid-sparing agents could not be assessed because the number of patients with non-steroid medications was low.

Conclusion

Inflammatory arthritis associated with MDS has various presentations, but joint destruction and serologic features are relatively rare. Steroids remain the main treatment regimen in these patients, and disease-modifying antirheumatic drugs are rarely used, most likely due to the associated cytopenia and concern about their impact on disease progression. Better treatment strategies for MDS-associated arthritis remain to be identified in the era of the new MDS agents.

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