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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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, WHO = World Health Organization.

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 unilineal dysplasia, RS3PE = remitting seronegative symmetrical synovitis with pitting edema, SNFMI = Société Nationale Française de Médecine Interne.
### TABLE 1. Baseline Characteristics and Follow-Up of Patients in the French Study

| Characteristics          | 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%)             |
| 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%)                     | 4 (21%)              | 3 (27%)               | 2 (22%)            | 4 (21%)            |
| Hydroxychloroquine       | 13 (60%)                    |                      |                       |                    |                    |
| Salazopyrin              | 26 (121%)                   |                      |                       |                    |                    |
| 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<sup>3</sup>) | 163 [62–657]              | 114 [50–242]         | 233 [75–250]          | 150 [40–244]       | 75 [12–146]*       |
| Neutrophils (n/mm<sup>3</sup>) | 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–I]            |
| 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).

*<i>p < 0.05 versus baseline.</i>

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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; 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), metatarso-phalangeal 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. 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. The International Prognostic Scoring System (IPSS) was retrospectively assessed, including the extent of cytopenia, cytogenetics, and the percentage of blasts in the bone marrow. The response of MDS to treatment was retrospectively defined according to the 2006 International Working Group criteria.

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). 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 polyarthritic 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

| Stable MDS or MDS-treatment response | MDS acceleration or absence of MDS-treatment response |
|--------------------------------------|-----------------------------------------------------|
| N=13                                 | N=8                                                 |

**FIGURE 1.** Inflammatory arthritis outcome in relation to MDS evolution (data available for 21 of 22 patients).
| 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 | 74/M -48     | RAEB1-2                         | P           | 107/ +           | None                   | Yes | Prednisone | Remission    |           |                |             |               |                |
| George       | 1992 | 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        | 64/ -           | None                   | Yes | Prednisone | Aggravation  | Remission  | Steroid dependence |            |               |                |
| George       | 1992 | NA -13       | RAEB2                           | P           | 60/ -           | None                   | Yes | Prednisone | None         | Remission  | Recurrence     |            |               |                |
| Pajus        | 1992 | 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                           | P           | 35/ -           | None                   | None | None       | Stable       | Stable     | 36             | Remission    |               |                |
| Kuzmich      | 1994 | 64/M -9      | RCMD                            | P           | 52/ -           | None                   | Yes | Prednisone | Transfusions | AL         | 18             | Remission    |               |                |
| Kuzmich      | 1994 | 61/M +5      | P                               | 55/ -       | None            | None                   | None | NSAID      | None         | Steroid dependence |            |               |                |
| Pando        | 1995 | 59/M +2      | RAEB1-2                         | O           | 68/ -           | None                   | None | Prednisone | 30 mg/d     | None       | 6              | No response  |               |                |
| Chandran     | 1996 | 80/M +36     | RC                              | P           | 85/5 -          | None                   | Yes | Prednisone | Transfusion  | Stable     | 6              | Remission    |               |                |
| Chandran     | 1996 | 84/F -6      | RARS                            | P           | 71/ -           | 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 | Prednisone | 20 mg/d     | AL         | 12             | Remission    |               |                |
| Carvajal     | 1996 | 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          | Steroid dependence |            |               |                |
| Kaufman      | 1997 | 77/F Concomitant | RAEB1-2                       | O           | 121/ -          | None                   | None | Methylprednisolone | VP16       | AL         | 9             | Remission/relapses |            |               |                |
| Cuende       | 1999 | 48/M +3      | RAEB1-2                         | P           | 110/193 -       | None                   | None | Prednisone | Transfusions | Stable     | 6              | Remission    |               |                |
| Nam          | 1999 | 31/F +24     | RCMD                            | P           | +               | Yes                    | None | Prednisone, HC | Androgens, transfections | Aracytine | AL | 5 | No response |               |                |
| Soubrier     | 2002 | 77/M -12     | RAEB1                           | P           | 93/42 +         | None                   | Yes | Prednisone | 10 mg/d, HC |             |                |             |               |                |
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 \((n = 1)\).

**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 [15–40]. Another disease-modifying anti-rheumatic 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
| 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             | 72/F        | Concomitant                      | N   | 114        | NA        | RAEB2      | NA  | 15               | None         | Progression | 6             | Remission   |
| Kohli 1994             | 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          | 82/F        | -12                             | N   | 54         | NA        | RAEB2      | NA  | 15               | None         | Progression | 24            | Remission/relapses |
| Mok 1996              | 59/F        | Concomitant                      | N   | 140        | NA        | RAEB1      | 1   | 20               | Transfusions | Stable      | 19            | Remission   |
| Billstrom 1995         | 68/F        | -4                              | Y   | 105        | NA        | RAEB2      | 3.5 | 20               | Stable       | 4           | Remission     |
| Hubscher 1996         | 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         | 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         | 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.
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 $^{10}$Y$^20$E 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 $^{11}$Y$^{30}$E, 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 $^{8}$Y$^{36}$E. The median time between the diagnosis of arthritis and MDS was 5 months $^{1}$Y$^{24}$E; 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 $^{15}$Y$^{35}$ of prednisone. Complete arthritis remission was achieved in 22/65 cases (34%). The majority of patients had RAEB-1/$^j$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

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

| First Author/Years | Age/Sex (yr) | Time Relation Arthritis-MDS | Type of MDS | ESR (mm/h) | CRP (mg/L) | RF | ACPA | Erosion | Prednisone (mg/d) | Other Treatment | MDS Outcome | Follow-Up (mo) | Arthritis Outcome |
|---------------------|--------------|-----------------------------|-------------|------------|------------|----|------|---------|-----------------|----------------|-------------|----------------|-----------------|
| Hernandez-Beriain   | 26           | 88/M, M +2                  | RC          | 80         | NA         | Negative | NA   | None   | 15               | None           | None        | Stable         | 8               | Remission       |
| Manganelli          | 34           | 72/M, M Concomitant          | RAEB1       | 100        | 52         | Negative | NA   | None   | 20               | None           | None        | Stable         | 31              | Remission/relapse |
| Beyne-Rauzy         | 8            | 72/M, M Before MDS           | RAEB1-2     | NA         | 52         | Negative | NA   | None   | 20               | None           | None        | Stable         | 24              | Remission        |
| Paira               | 41           | 75/M, M +11                  | NA          | 60         | NA         | Negative | NA   | None   | 12               | None           | None        | NA             | 24              | Remission        |
| PR, RS3PE Case 1    | 81/M         | 81/M, M Concomitant          | RC           | NA         | 15         | Negative | NA   | None   | 10               | None           | None        | Stable         | 2               | Remission        |
| PR, RS3PE Case 2    | 77/M         | 77/M, M Before MDS           | RAEB2       | 50         | 10         | Negative | NA   | None   | 20               | None           | None        | Stable         | 10              | Remission        |
| PR, RS3PE Case 3    | 51/F         | 51/F, F Before MDS           | RAEB1       | 65         | 10         | Negative | NA   | None   | 65               | None           | None        | Stable         | 24              | Remission        |
| PR, RS3PE Case 4    | 89/M         | 89/M, M +6                  | RCMD         | 65         | 10         | Negative | NA   | None   | 65               | None           | None        | Stable         | 24              | Remission        |

Abbreviations: See previous tables.

**FIGURE 2.** Time between arthritis and MDS diagnoses in all patients.
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.3 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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### 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.
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