Autoimmune syndromes presenting as a paraneoplastic manifestation of myelodysplastic syndromes: clinical features, course, treatment and outcome

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Abstract

Autoimmune manifestations (AIM) are reported in up to 10-30% of myelodysplastic syndromes (MDS) patients; this association is not well defined. We present herein a retrospective chart review of single center MDS patients for AIM, a case discussion and a literature review. Of 252 MDS patients examined, 11 (4.4%) had AIM around MDS diagnosis. International Prognostic Scoring System scores were: low or intermediate (int)-1 (n=7); int-2 or high (n=4). AIM were: culture negative sepsis (n=7); inflammatory arthritis (n=3); vasculitis (n=4); sweats; pericarditis; polymyalgia rheumatica (n=2 each); mouth ulcers; pulmonary infiltrates; suspicion for Behcet's; polychondritis and undifferentiated (n=1 each). AIM treatment and outcome were: prednisone +/- steroid sparing agents, n=8, ongoing symptoms in 5; azacitidine (n=3), 2 resolved; and observation, n=1, ongoing symptoms. At a median follow up of 13 months, seven patients are alive. In summary, 4.4% of MDS patients presented with concomitant AIM. MDS should remain on the differential diagnosis of patients with inflammatory symptoms.

Introduction

The myelodysplastic syndromes (MDS) are clonal hematopoietic disorders of ineffective hematopoiesis and risk of acute myeloid leukemia (AML) progression.[1] Prognosis is determined by the International Prognostic Scoring System (IPSS) and other scores.[2] Mutations in the pluripotent hematopoietic stem cell occur in MDS, with disruption of RNA splicing, ribosomal proteins, telomeres, microRNA expression, and DNA methylation.[3-6] Reports suggest an association between MDS and immune dysregulation.[7] Cytokine dysregulation and impaired cellular immunity have been noted in MDS initiation, development, and progression.[8] Autoimmune (AI) symptoms have been reported in up to 10-30% of MDS patients.[9-11] Patients with AI disorders or receiving immunosuppressive agents are more likely to be diagnosed with MDS.[12]

Paraneoplastic inflammatory syndromes concomitant with MDS diagnosis have also been reported.[9,13-15] To better understand the incidence and outcomes of patients with MDS and AI disorders, we conducted a retrospective chart review of patients with MDS, looking for symptoms of AI disorders.

Materials and Methods

Myelodysplastic syndromes patients were identified from a single-center MDS database. Charts were reviewed for the presence of autoimmune manifestations (AIM) within a 3-year period prior to or following the diagnosis of MDS, treatment and outcome. Patients with a longstanding history of connective tissue disorders were excluded. The term culture negative sepsis was used to describe fevers or drenching sweats with a negative workup for infectious and other causes such as drug fevers. Although these symptoms may be a manifestation of systemic vasculitis, the latter term was reserved for patients with biopsy-proven vasculitis. Cases that are illustrative of AIM were selected for presentation.

Survival analyses were conducted by the log-rank method using SPSS for Windows, version 20. This review was conducted in accordance with the requirements of the institutional Research Ethics Board.

Results

Of 252 MDS patients, eleven (4.4%) had AIM presenting at or shortly before MDS diagnosis. Baseline and MDS characteristics, treatment and outcome are shown in Table 1. Eight patients were documented to have had a workup by the rheumatology service, and seven were followed regularly by rheumatology; all rheumatology-assigned diagnoses of autoimmune diseases are listed in Table 1.

Of seven patients with culture negative sepsis, all underwent an extensive workup for infectious causes, five by the Infectious Diseases service. Three received intravenous antibiotics with no improvement. Other causes of fevers, such as medications, were considered but none identified. All seven had at least one bone marrow aspirate and biopsy performed during a symptomatic episode, with no hemophagocytosis seen. Four of these patients had 3 bone marrows performed, and one had more than ten done in two countries over a period of more than 7 years. Two patients had ferritin levels done; the maximum level was 1200 ng/mL. None of the patients had splenomegaly on physical examination, and one underwent CT scanning of the abdomen because of abdominal pain; the spleen was normal on imaging.

At a median follow up of 13 (4-87) months, seven patients are alive, six with stable MDS and one is undergoing allogeneic myeloablative hematopoietic stem cell transplantation (HSCT). Four patients died; causes were: MDS progression, n=2; infection, n=1; and unknown, n=1.

Of four patients with int-2 or high IPSS risk MDS, three were treated with azacitidine. One patient receiving azacitidine did not respond, there was one early infectious death, and the third is undergoing HSCT.

Overall survival (OS) analyses were performed comparing MDS patients with AIM to those without AIM. The OS of seven lower IPSS risk patients with AIM were compared to 204 lower risk MDS diagnosed over the same time

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Key words: Autoimmune; myelodysplastic syndromes; HDS.

Contributions: BTW reviewed the charts and wrote the paper; LMF, critically revised the paper; HAL, supervised the chart review, revised the paper and performed statistical analyses.

Conflict of interest: BTW was supported by a Summer Studentship from Celgene. LMF has consulted for Novartis and Janssen; has received research funding from Novartis, Incyte, Gilead and Promedior; and has received honoraria from Novartis. HAL has received research funding and honoraria from Novartis, Celgene and Alexion; has received an educational grant from Celgene; and is a member of the Exjade Speaker's Bureau.

Poster presentation: Norman Bethune Symposium, Vancouver, BC, November 13, 2014. Canadian Conference on MDS, Banff, AB, September 12-13, 2014.

Received for publication: 20 February 2016.
Revision received: 30 April 2016.
Accepted for publication: 2 May 2016.

Hematology Reports 2016; 8:6480
doi:10.4081/hr.2016.6480

period. The median follow up of all lower risk patients was 27.3 (0.5-161) months. There was no significant difference in OS between groups; all seven (100%) patients with AIM are alive compared to 166 (78.7%) patients without AIM, and the median OS was not reached at 43 months compared to 78.8 months, respectively (P=NS).

Of higher IPSS risk patients, we restricted the analysis to patients diagnosed since azacitidine was available in Canada and compared three patients with AIM receiving azacitidine to 29 patients without AIM, but also receiving azacitidine. The median follow up of this group was 7.3 (0.5-46) months. There was no significant difference in OS between groups (P=NS).

Of eight patients receiving immunosuppression for AIM, one died of AML progression at 4 months, one died of progressive (higher IPSS risk) MDS in the context of stopping azacitidine at 6 months, and one died suddenly of unknown causes 32 months from MDS diagnosis. The remaining five patients had stable MDS at a median of 14 (5-23) months from MDS diagnosis. Four of these patients were followed by Rheumatology and the fifth was given immunosuppressive medications by emergency room physicians for pericarditis. Both patients with systemic vasculitis had this diagnosis made on biopsy, one on open lung biopsy, and one on skin biopsy. Only one patient, without biopsy proven vasculitis but with culture negative sepsis, had anti-neutrophil cytoplasmic antibody (ANCA) levels done, which were negative.

Patient #1

A 31 year-old woman presented with fatigue and cytopenias. White blood cell (WBC) count was 3.9×10^9/L, neutrophils 1.8×10^9/L, hemoglobin (Hb) 125 g/L and platelet count (PLTS) 100×10^9/L. Peripheral blood morphology showed macrocytosis. Antinuclear antibody (ANA) was positive at a 1:320 dilution. She did not fulfill criteria for systemic lupus erythematosus (SLE) and was observed. Neutropenia and thrombocytopenia persisted and mild anemia developed (Hb 119 g/L). A bone marrow aspirate and biopsy (BMBx) showed erythroid dysplasia, 1% blasts and trisomy 8. A diagnosis of refractory cytopenia with unilineage dysplasia (RCUD) was made and the IPSS was int-1. The patient declined HSCT and yearly BMBx's remained stable. Within one year of MDS diagnosis, she developed a rash to sun exposure. She experienced culture negative fevers and mouth ulcers suspicious for Behcet's disease. Symptoms are ongoing 9.75 years from MDS diagnosis despite the use of non-steroidal anti-inflammatory medications. AIM nearly completely abated during three pregnancies.

Table 1. Autoimmune manifestations of myelodysplastic syndromes in 11 patients: clinical features, treatment and outcome.

Characteristic	N (%) /Median (range)
Age (years)	68 (34-84)
Gender (male)	7 (64)
FAB* or WHO MDS diagnosis	
RCUD	2
RCMD-RS	2
RA	1
RARS	1
RCMD	1
RAEB-t°	1
MDS-NOS	1
CMML-2	1
IPSS risk	
Low	3
Intermediate-1	4
Intermediate-2	3
High	1
IPSS cytogenetics group	
Good	6
Intermediate	2
Poor	3
Significant conditions	
No	8
Yes[#]	3
MDS treatment	
Observation	5
Supportive care[§]	3
Azacitidine	3
MDS outcome	
Stable	6
Good response	1
Died^	4
Autoimmune manifestation (AIM)	
Culture negative sepsis	7
Inflammatory arthritis	3
Systemic vasculitis	2
Cutaneous vasculitis	1
Polymyalgia rheumatica	2
Connective tissue disorder NOS	2
Polychondritis	1
Pericarditis	2
AIM months in relation to MDS diagnosis	1 (-38-34)
Serological abnormalities	
Positive ANA	6
Elevated CRP	5
Elevated ESR	2
Monoclonal paraprotein	1
Positive RF	1
AIM treatment	
Observation	3
Prednisone	8[$]
Methotrexate	4
Hydroxychloroquine	4
Azathioprine	2
Gold	1
Chlorambucil	2
Dapsone	1
AIM outcome	
Resolution of all symptoms	3
Partial resolution of symptoms	4
Persistent symptoms	4

ANA, anti-nuclear antibody; CMML; chronic myelomonocytic leukemia; CRP, C-reactive protein; EB-t; excess blasts in transformation; ESR, erythrocyte sedimentation rate; FAB, French-American-British; IPSS, International Prognostic Scoring System; MD, multilineage dysplasia; MDS, myelodysplastic syndrome; NOS, not otherwise specified; RA, refractory anemia; RS, ring sideroblasts; RF, rheumatoid factor; t-, treatment related; UD, Unilineage dysplasia. *According to era of MDS diagnosis; °t-MDS; [#]myasthenia gravis and systemic lupus erythematosus; psoriatic arthritis, polychondritis and vasculitis; well-controlled HIV infection; n=1 each. The course of the HIV-positive patient has been published in detail (Williamson BT & Leitch HA, 2016). [§]Erythropoietin, n=2; red blood cell transfusions + iron chelation therapy, n=1. ^MDS progression, n=2; complications of treatment, n=1; unknown cause, n=1. [$]7 in combination with other agents.

Patient #2

A 77 year-old man presented with fatigue. Hb was 127 g/L, neutrophils 1.8×10^9/L, and PLTS 133×10^9/L. ANA titer was 1:80. A BMBx showed trilineage dysplasia, <5% blasts and a normal male karyotype. A diagnosis of refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS) was made and the IPSS was int-1.

Six months after MDS diagnosis he developed progressive stiffness of the thighs, shoulders and neck. Workup revealed a positive rheumatoid factor (RF), C-reactive protein (CRP) of 44.2 mg/L (>7 mg/L indicates inflammation) and erythrocyte sedimentation rate (ESR) of 34 mm/hr (upper limit of normal 10 mm/hr). He was diagnosed with rheumatoid arthritis (RA) with a polymyalgia rheumatica (PMR)-type onset. He received 40 mg prednisone daily with near complete resolution of symptoms, and was transitioned to hydroxychloroquine and methotrexate.

Patient #3

A 70 year-old man presented with a Hb of 82 g/L. A BMBx showed erythroid dysplasia with ring sideroblasts, no increase in blasts, and deletion of chromosome 7. A diagnosis of refractory anemia with ring sideroblasts (RARS) was made and IPSS was int-1. He received blood transfusion support.

For 12 months prior to MDS diagnosis, he experienced intermittent swelling around the eyes and ears, fatigue and arthralgias. Five months after MDS diagnosis, he developed a skin rash; biopsy showed leukocytoclastic vasculitis. He received 50 mg prednisone daily, with marked improvement, allowing a taper to 10 mg daily, which controlled symptoms. He died suddenly thirty-two months from MDS diagnosis.

Patient #4

A 66 year-old man presented with pancytopenia. WBC count was 2.5×10^9/L, neutrophils 0.3×10^9/L, Hb 129 g/L, and PLTS 143×10^9/L. The ANA was 1:160. A BMBx was non-diagnostic. Five months later, he developed widespread myalgias and swelling of the hands. He was diagnosed with PMR and inflammatory arthritis not otherwise specified (NOS). Six months later, he developed hyperkeratotic patches on the scalp and hands. Skin biopsies showed a connective tissue disorder NOS. The diagnosis was amended to mixed connective tissue disorder, and he received azathioprine, hydroxychloroquine and prednisone. Five months later, the ESR was 64 mm/hr.

Three months later, he experienced three episodes of culture negative sepsis. After an additional two months, dysplastic features in neutrophil precursors were seen. A repeat BMBx showed <1% blasts, increased cellularity and remained non-diagnostic. Cytogenetic analysis was normal male karyotype. Eight months from the second BMBx, the diagnosis was amended to MDS following a review of the previous BMBx at our center. The IPSS was low risk. Five months later, a third BMBx indicated no MDS progression, and cytogenetics remained normal.

This patient has ongoing arthritic symptoms. Following 15 months of treatment with immunosuppressive medications, culture negative fevers have not recurred.

Patient #5

A 39-year-old man presented with drenching sweats and chest pain, the latter diagnosed as pericarditis and treated with aspirin and colchicine. One week later, he developed abdominal pain suspicious for Behcet's disease. A CBCD revealed a Hb of 110 g/L and a leukoerythroblastic picture. WBC count was 5.9×10^9/L, neutrophils 1.1×10^9/L, PLTS decreased (count unavailable due to clumping). A BMBx showed multilineage dysplasia, ring sideroblasts, 4% blasts and a complex karyotype. A diagnosis of RCMD-RS was made and the IPSS was int-2. He was initiated on azacitidine. Four months later, he developed culture-negative sepsis, three episodes in total. He also had a widespread, recurrent petechial rash without significant thrombocytopenia. A second BMBx one month after cycle two of azacitidine showed no MDS progression. He received four cycles of azacitidine in total with hematologic improvement in all lineages. He continues to suffer from fatigue and episodes of pericarditis; however, the other symptoms abated. He is undergoing HSCT.

Discussion and Conclusions

Reports suggest an association between AI manifestations and MDS, including: acute systemic vasculitis; chronic AI syndromes; connective tissue disorders; immune-mediated cytopenias; and serological abnormalities.[9,13-21] Inflammatory syndromes may precede or follow the diagnosis of MDS.[9,19,22]

Cytokines implicated in MDS include tumor necrosis factor alpha (TNF-α) and transforming growth factor beta (TGF-β), which result in upregulation of proinflammatory and myelosuppressive cytokines, respectively.[23,24] Interferon regulatory factor-1 (IRF-1) is involved in activities including inflammatory responses, and IRF mRNA was increased in MDS patients with AIM.[10] Immune cells that may be involved in AIM include natural killer (NK) cells and regulatory T-cells.[25,26]

The prognostic impact of AIM in MDS is a matter of debate. In one study, the median survival of MDS patients with no AIM was 25 months compared to 9 months in patients with AIM.[9] Acute vasculitis had a particularly poor prognosis, with a median survival of only 6 months. However, this study did not take into account the IPSS score. In another study that considered IPSS score and treatment, patients with AIM (n=13) did not have an inferior prognosis to those without (n=57).[10] We separated our patients into lower IPSS risk, and higher risk receiving azacitidine, and compared the outcomes of those with and without AIM. In both instances we did not find a significant difference in OS between groups, though small numbers limits interpretation of these analyses. Supportive treatment of AIM in MDS requires careful consideration, as immunosuppressive medications (ISM) may increase infectious risk and exacerbate cytopenias. In one study, however, 26 of 27 of MDS patients with AIM responded favorably to ISM but only 6 experienced sustained AIM remission.[27] There are reports of MDS progression with immunosuppression,[28] but on the other hand, immunosuppressive therapy such as anti-thymocyte globulin (ATG) and cyclosporine may result in responses in some MDS patients.[7] Given the uncertain safety of ISM for the treatment of AIM in MDS, these medications should be used with caution and patients monitored closely.

Treatment of MDS may improve AIM. In one series of 22 patients with AIM receiving azacitidine for MDS, 19 (86%) had an AIM response within 3-6 azacitidine cycles, allowing discontinuation of ISM.[29] Azacitidine is thought to act in this regard by increasing the number of FOXP3+ regulatory T-cells and inhibiting CD4+ T-cells.[13,30]

In six patients with AIM in MDS relapsed or refractory to steroid treatment, 5 had a response to lenalidomide, with 3 complete remissions.[31] There are reports, however, implicating lenalidomide in increased AIM.[32] Lenalidomide modulates the function of NK cells, monocytes, dendritic cells, and T-cells, and increases cytokines involved in attenuating inflammatory responses.[25,26]

The findings in our patients are consistent with other reports, with AIM occurring concomitant with MDS diagnosis in 4.4%, in patients with a median age of 68 years, 9 of 11 having adverse karyotype, and present in all IPSS risk groups.[9-11,16,33] Though this percentage is lower than in previous reports, we restricted the analysis to patients presenting with AIM around the time of MDS diagnosis and excluded patients with longstanding autoimmune disorders.

In conclusion, MDS should remain on the differential diagnosis of patients undergoing work up for AIM. Similarly, MDS patients with AIM should be identified as symptoms may respond to therapy with immunosuppressive medications or specific MDS treatments.

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