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Myelodysplastic Syndromes and Autoimmune Diseases - Case Series and Review of Literature

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Abstract

Our objective was to recognize the association of autoimmune disease (AD) in patients with myelodysplastic syndromes (MDS) and understand how this association could affect prognosis and management of both diseases. We describe our cohort of 10 patients and 34 patients reported in the English literature in addition to ten cohort studies. Interestingly, four cases showed improvement in AD after 5-azacitidine treatment. The mechanism(s) of the association between AD and MDS are discussed. Treatment could be targeted against AD, MDS or both, though based on recent reports, treating MDS with hypomethylating agents alone could improve the associated AD.

Keywords

myelodysplastic syndrome; autoimmune diseases; outcome; hypomethylating agents; treatment

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Introduction

Approximately 10–20% of patients with myelodysplastic syndrome (MDS) present with autoimmune diseases (AD) which can be challenging to recognize. The autoimmunity is believed to be triggered by the increased apoptosis in the dysplastic bone marrow. Recent evidence suggests that both diseases are characterized by dendritic (1) and T-cell (2) abnormalities. AD presentation varies from clinical syndromes such as vasculitis, lupus and rheumatoid arthritis to laboratory abnormalities such as thrombocytopenia, hemolytic anemia and autoantibodies (3). We encountered ten cases of adults with MDS and AD at Roswell Park Cancer Institute (RPCI) from 2007 to 2010 out of 123 (8.1%) cases diagnosed during the same time period. To gain more insight into the association of MDS and AD, we also examined the English literature on all MDS and AD cases between the years 1991 to 2011 with reported clinical features.

Patients and Methods

Data on ten MDS patients with AD diagnosed at RPCI, Buffalo were reviewed on IRB-approved institute protocol. We attempted to compare these patients with a similar group of patients with MDS without AD but could not identify young female patients with MDS without AD. In addition, 34 MDS and AD cases described in the literature were also reviewed. Cases with incomplete clinical features were excluded. We recorded patients' age, gender, whether the presentation was synchronous or metachronous, MDS pathology, karyotype, AD characteristics, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-mitochondrial antibody (AMA), antinuclear antibody (ANA), complement (C3) 3, complement 4 (C4), anti-double strand DNA antibodies (anti-DsDNA), rheumatoid factor (RF), cold agglutinins, treatment of MDS/AD, outcome of MDS/AD and overall survival. Finally, we performed a Medline search and identified ten large series describing MDS and AD patients.

Results

Patient Characteristics

As shown in Tables 1 and 2, ten large series (3–12) encompassing a total of 2,466 patients demonstrated that 15% (range, 7%–25%) of MDS patients had AD. Five of the ten cohorts listed the laboratory characteristics of patients with both MDS and AD (Table 3). The median age of the patients was 62 years and 60% of the patients were males.

Ten patients from RPCI were identified to have MDS and AD between 2007 and 2010. Patients' basic characteristics, AD manifestations and outcomes were analyzed along with 34 cases from our MEDLINE search [Tables 4, 5 (8, 13–37)]. As seen in Table 4, most of these patients were males (70%) and the median age at diagnosis of MDS was 59 years. The presentation of MDS and AD was synchronous in 56% of the patients. In patients with asynchronous presentations, the preceding diagnosis distributed equally whether it was MDS or AD first.

Characteristics of AD

The most prevalent manifestations in the ten series (Table 1) were vasculitis syndromes (40%) followed by seronegative arthritis (27%) and neuropathy (24%). Vasculitis varied in presentation from small vessel disease such as leucocytoclastic vasculitis, skin vasculitis and microscopic polyangiitis to medium vessel diseases such as anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis and finally large vessel disease such as temporal arteritis and Takayasu's vasculitis. Rare cases of isolated CNS vasculitis were also

described. The most prevalent manifestations among the 44 cases were vasculitis followed by seronegative arthritis and skin lesions (Table 4).

As shown in Table 3, the most prevalent laboratory abnormalities, in the five of ten large series with reported laboratory results, were hypergammaglobulinemia (35%) and ANA positivity (30%). The most common laboratory abnormalities associated with AD in the 44 cases were elevated ESR (88%) and CRP (78%) (Table 5). The difference in the laboratory abnormalities between the five of ten series with reported laboratory results and the case reports along with our series (44 patients) may reside in the fact that not all studies addressed the same spectrum of laboratory abnormalities.

Characteristics of MDS

As shown in Table 2, refractory anemia was the most common type of MDS (39%) in the ten large series and also among the 44 case series (36%). Four out of the cohort studies documented the karyotype for a total of 56 patients with both MDS and AD; 41% of the patients had normal karyotype followed by chromosome 7 abnormalities in 16% of the patients. Trisomy 8 (38) and del(5q) (10%) were less common (data not shown). Among the 44 cases reviewed, the most common cytogenetic presentation was normal diploid karyotype in 44% followed by having two or more abnormalities (13%). As a sole deletion, del(5q) was more common (11%) in comparison to del(20q) (9%).

It was difficult to draw a conclusion on International Prognostic Scoring System (IPSS) (39) from the available data since some of the series predate the IPSS; Dalamaga et al (9) reported six patients with low risk IPSS and 15 patients with high risk IPSS of 21 patients with MDS and AD that were reported in a cohort of 84 MDS patients. Concerning treatments, the patients received an assortment of modalities, all without hypomethylating agents, and therefore specific conclusions about the treatments could not be drawn.

Finally, transformation to acute myeloid leukemia occurred in 25% of the patients in both the large series and the 44 cases, which is not significantly different than the frequency of disease transformation in MDS without AD (40) in the pre-hypomethylating agents era.

Prognosis

Data on the prognosis of MDS patients who develop AD is scarce. Enright et al (4) showed that the median survival for patients with MDS (from MDS diagnosis) was 25 (range 3.5–142) months while the median survival for patients with MDS and AD was only 9 (range 1–143) months. In some of the patients in that series, a rapid deterioration occurred with the onset of AD. The median survival in MDS patients from diagnosis of AD was as short as 6 (1–143) months. Interestingly, those with chronic or isolated AD lived longer [23 (range 3–124) months]. The causes of death ranged from worsening pulmonary infiltrates to intracranial hemorrhage due to flare of vasculitis, gastrointestinal hemorrhage and sepsis. Okamoto et al (5) also showed that the outcome of MDS patients with AD was significantly worse than the outcome of MDS patients without AD, though the cause of death in this series was infection or leukemic progression. Similarly, Dalamaga et al (9) showed that MDS with AD was about 3.59 times more likely to be in the high-risk MDS category than in the low-risk range. Finally, Castro et al (8) also showed a worse outcome for MDS with AD with three of 16 patients dying after one year of follow-up. However, Marisavljević et al (7) showed similar incidence of low-risk MDS among patients with and without AD. Of note, the study (7) focused more on autoimmune serologic abnormalities rather than clinical presentations of AD in patients with MDS.

Discussion

AD occurring in the setting of MDS is important to recognize not only for the purpose of knowledge *per se* but also in regard to prognosis and treatment options. Therefore, our discussion concentrates on these latter issues.

Since most of these data precede the use of hypomethylating agents in MDS treatment, and observations from others (41) and our own (42) suggest that treating MDS with a hypomethylating agent may improve the outcome of AD, it is important to see whether AD will continue to be a negative prognosticator in MDS in the hypomethylating era. The role of hypomethylating agents as immunomodulators is still poorly understood. It could be explained by the effect noted on T-cells activation and proliferation, decrease in proinflammatory cytokines, and the up-regulation in genes such as p53 that lead to cell-growth arrest. The immunomodulatory concept was shown by using 5-azacitidine to control a graft-versus-host disease in a fully mismatched allogeneic transplant mouse model (43).

On the other hand, when examining the effect of immunomodulation on the outcome of AD, we noted that two patients from RPCI were treated with lenalidomide for their MDS, they both had bronchiolitis obliterans organizing pneumonia; one patient's pulmonary symptoms continued to deteriorate and the other had stable mild symptoms with the use of corticosteroids. It is difficult to draw a conclusion about lenalidomide from this limited number of patients. While improvement of AD symptoms has been observed in MDS patients post allogeneic stem cell transplantation (two patients from RPCI) or umbilical cord transplant (17); other reports suggested that lenalidomide is a possible cause for lymphocytic/eosinophilic immune myocarditis, hypersensitivity pneumonitis or autoimmune hemolytic anemia (44–47) which should raise the possibility of exacerbating autoimmunity when lenalidomide is used in MDS.

The effect of immunosuppression on MDS was studied by Enright et al (4) where he identified 30 patients with AD in a cohort of 221 MDS patients. As most of the AD responded to immunosuppression (27 patients had corticosteroids, two sulfasalazine, one azathioprine, one cyclophosphamide and one with both azathioprine and cyclophosphamide). The authors noted improvement of peripheral cytopenia in ulcerative colitis patients that were responding to sulfasalazine. They also noted improved cytopenia in six patients treated with immunosuppression without using any MDS-specific therapy; and in the case of one patient with refractory anemia, cytogenetic clonal abnormalities disappeared with immunosuppressive therapy and the patient stayed alive after 13 years of follow up. The survival in the group of patients with hematologic improvement (n=6) to immunosuppression was better when compared to non-responders (59 vs. 9 months, P=0.02). Interestingly, Giannouli et al(3) did not find a similar association in a similarly designed study.

A crucial point in understanding the effect of AD on MDS outcome and for planning an appropriate treatment would be improved insights into the underlying pathophysiology of AD in the context of MDS. Kiladjian et al (2) have suggested that ineffective hematopoiesis in MDS causes increased apoptosis of dysplastic precursor cells in the bone marrow exposing tumor neo-antigen(s) (still unknown) that evoke an adaptive immune response. Support for this hypothesis comes from the fact that activated T-cells with clonal expansion ability were found in the majority of MDS patients studied. Although the exact significance of these T-cells remains unclear, differences in their percentages and their expansion capabilities between patients with MDS and AD and those with MDS without AD were detected. These authors demonstrated that the percentage of Gamma-Delta T-cells [which are involved in immune reactions against tumor cells by producing tumor necrosis factor

alpha (TNF-α) and interferon gamma (IFN-γ)] were significantly lower in MDS patients with AD compared to either healthy donors or MDS patients without AD and were in the same low range as in patients with AD without MDS. Furthermore, they demonstrated that interleukin (IL)-2 and bromohalohydrin pyrophosphate, which stimulate expansion in 100% of T-cells, were only able to expand Gamma-Delta T-cells in 60% of MDS patients and 70% of the non-responding patients had AD, suggesting that the lack of response is related to the presence of AD (2).

Another cell population involved in MDS etiology is the regulatory T-cells (T-Regs, $CD4^+$/$CD25^{high}$/$FOXP3^+$) (48). T-Regs are usually involved in maintaining immune tolerance and their expansion, in malignant disease, often results in suppression of host anti-tumor responses. The role of T-Regs in various autoimmune diseases is still unclear. While some authors such as Kordasti et al (48) demonstrated that MDS patients with a high IPSS had higher T-Reg percentages which allowed clonal expansion and disease progression when compared to MDS patients with low IPSS; others (49, 50) observed a higher percentage of functional T-Regs in patients with AD. We (42) therefore analyzed the percentages of T-Regs in a patient with MDS and AD before and after 5-azacitidine treatment. Our results demonstrated a decrease in TRegs following nine cycles of 5-azacitidine treatment along with clinical improvement in both MDS and AD. The key seems to be related to understanding the various immune effects of hypomethylating agents on this subset of cells. In both *in-vivo* and *in-vitro* studies, these agents demethylate the FOXP3 promoter thus increasing the number of T-Regs which could be beneficial in low risk MDS where T-Regs control seems to be lacking in addition to decrease in IFNγ production. On the other hand, the same agent could enhance *in-vitro* IFN-γ production by demethylation IFN-γ promoter (51). These discrepancies also support that there is more to define when studying T-Regs physiology in MDS and autoimmunity. Finally, concomitant treatment with corticosteroids could play a role in affecting the number of T-Regs in these cases.

Also, it has been shown that monocyte-derived dendritic cells (MoDCs) from MDS patients are numerically and functionally defective (1, 52). DCs are considered one of the most potent antigen presenting cells (APC), They usually differentiate from circulating monocytes under “danger” mediators' effect such as lipopolysaccharadies, TNF-α or other cytokines. *In-vitro*, DCs are being generated from peripheral blood monocytes by culturing with IL-4 and granulocyte-macrophage colony-stimulating factor. When compared with healthy donor samples, MDS patients' MoDC had impaired/low differentiation and low endocytic capacity. They were also suggested to be derived from the same MDS clone (95% of DCs from 2 patients with 5q deletion had the same clonal abnormalities). For all that, it is believed MoDCs in these patients are ineffective in clearing the increased apoptotic bodies in the dysplastic bone marrow, which could attribute to triggering autoimmune manifestations.

Finally, interferon regulatory factor-1 (IRF-1) was previously suggested to be a transcription activator for IFN-β and to activate parts of the immune response (IL-2 and Th1 differentiation); when truncated IRF-1 becomes non-functional and involved in myelodysplasia (53, 54). Its loss was shown to cause leukemogenesis (55). Giannouli et al (56) have studied its role as a possible link between autoimmunity and myelodysplasia by comparing IRF-1 full length mRNA (IRF-1 FL) (as a surrogate for alternative splicing that gives rise into nonfunctional IRF-1) in samples from MDS and AD, MDS without AD, vasculitis and normal control patients. They confirmed the low expression of IRF-1 FL in MDS samples; those with MDS and AD had high expression of IRF-1 FL similar to those with vasculitis alone (without MDS). With those findings it was concluded that inhibiting IRF-1 could play a therapeutic role in controlling autoimmunity in MDS patients.

In summary, though the exact mechanism(s) underlying MDS and AD are not well established, it is important to look for early signs of autoimmunity in MDS patients. Treatment options include treating MDS only as suggested by others (41) and our observation (42) of treating both diseases concomitantly with 5-azacitidine.

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Table 1

Clinical presentations of AD associated with MDS from ten series

Presentation	Ref# 7	Ref# 8	Ref# 11	Ref# 5	Ref# 6	Ref# 4	Ref# 3	Ref# 10	Ref# 9	Ref# 12	Median (%)
AD (% of MDS)	20/284 (7)	16/162 (10)	8/82 (10)	16/153 (10)	10/83 (12)	30/221 (14)	13/70 (19)	16/80 (20)	21/84 (25)	574/2471 (23)	15
Vasculitis (% of AD)	5/20 (25)	7/16 (43)	2/8 (25)	-	6/10 (60)	20/30 (66)	7/13 (53)	8/16 (50)	6/21 (28)	21/574 (4)	40
Seronegative arthritis (% of AD)	-	7/16 (43)	5/8 (62)	-	-	1/30 (3)	-	-	-	5/574(1)	27
Neuro (% of AD)	-	8/16 (50)	-	-	-	7/30 (23)	3/13 (23)	-	-	5/574(1)	24
BOOP and IPF (% of AD)	-	-	-	-	-	9/30 (30)	2/13 (15)	1/16 (6)	-	-	15
GN (% of AD)	-	2/16 (12)	-	-	-	5/30 (16)	1/13 (7)	-	-	-	12
RA (% of AD)	4/20 (20)	1/16 (6)	2/8 (25)	-	-	1/30 (3)	-	1/16 (6)	-	150/574 (26)	12
Sweet's (% of AD)	2/20 (10)	-	-	5/16 (31)	1/10 (10)	-	-	2/16 (12)	2/21 (10)	-	10

Only AD manifestations >5% are depicted in the table

Data are not shown for: SLE and Raynaud's (4.6% each of all AD); RP, Sjogren's, photosensitivity, myositis, PMR, Panniculitis (4% each of all AD); IBD and PBC combined 3.3%; Thyroditis 2.6%; Vitiligo and Erythema Nodosum (1.3% each of all AD). Anderson had 55/574 MDS with PMR (not shown).

Abbreviations: AD, Autoimmune disease; BOOP, Bronchiolitis obliterans organizing pneumonia; GN, Glomerulonephritis; IBD, Inflammatory bowel disease; IPF, Idiopathic pulmonary fibrosis; MDS, Myelodysplastic syndrome; PBC, Primary biliary cirrhosis; PMR, Polymyalgia rheumatic; RA, Rheumatoid arthritis; RP, Relapsing polychondritis; SLE, Systemic lupus erythematous

Table 2

MDS characteristics in patients with MDS and AD from six series

Presentation	Ref# 8	Ref# 5	Ref# 6	Ref# 4	Ref# 3	Ref# 9	Median (%)
AD (% of MDS)	16/162(10)	16/153(10)	10/83(12)	30/221(14)	13/70(19)	21/84 (25)	12
Median age (years)	67	48	66	63	67	NA	62
Male (%)	12/16(75)	4/16(50)	7/10(70)	16/30(53)	7/13(53)	NA	60
RA (%)	3/16(18)	9/16(56)	3/10(33)	15/30(50)	6/13(46)	5/21(24)	39
RARS (%)	2/16(12)	0	0	3/30(10)	1/13(7)	3/21(14)	7
RAEB (%)	2/16(12)	2/16(12)	3/10(33)	7/30(23)	2/13 (14)	4/21 (19)	18
RAEB-t (%)	1/16(6)	5/16(31)	1/10(10)	2/30(6)	2/30(6)	5/21(24)	15
CMML (%)	1/16 (6)	0	0	1/30 (3)	2/30(6)	4/21(19)	7
Cytogenetics *	Normal	Normal	Complex	Del(5q)	NA	NA	

Abbreviations: AD, autoimmune diseases; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; NA, not available; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-t, refractory anemia with excess blasts in transformation; RARS, Refractory anemia with ringed sideroblasts;

* Only most common cytogenetic finding is listed.

Table 3

Laboratory abnormalities in patients with associated MDS and AD from five series

Presentation	Ref# 3	Ref# 9	Ref# 4	Ref# 5	Ref# 7	Median (%)
AD (% of patients)	13/70 (19)	21/84 (25)	40/221 (18)	N/A	N/A	19
Hypergammaglobulinemia (% of AD)	10/13 (76)	Present †	9/40 (22)	50/128 (39)	90/284 (31)	35
ANA (% of AD)	4/13 (30)	6/21 (28)	14/40 (35)	35/115 (30)	67/284 * (23)	30
RF (% of AD)	3/13 (23)	18/21 (85)	2/40 (5)	16/115 (14)	*	18.5
Hypocomplementemia (% of AD)	-	-	7/40 (17)	-	-	17
DAT (% of AD)	3/13 (23)	6/21 (28) ‡	6/40 (15)	13/108 (12)	14/2 (5)	15
Cryoglobulins (% of AD)	-	-	5/40 (12)	-	-	12
Antiphospholipids antibodies (% of AD)	-	-	4/40 (10)	-	-	10
Hypogammaglobulinemia (% of AD)	1/13 (7)	-	2/40 (5)	11/128 (8)	42/284 (14)	7.5
Anti DsDNA (% of AD)	-	-	-	8/110 (7)	-	7
AMA (% of AD)	1/13 (7)	-	1/40 (2.5)	-	*	4.75
Antiplatelets antibodies (% of AD)	1/13 (7)	-	-	2/153 (1)	-	4

ASMA was reported in one study in 1/40 patients (2.5%)

Abbreviations: AD, autoimmune disease; AMA, anti-mitochondrial antibodies; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; DAT, direct antiglobulin test; RF, rheumatoid factor;

* Combined ANA, RF and AMA reported values

† Only mean gammaglobulin value is available

‡ Higher than weak positive result

Table 4

Patient characteristics: N=44 (10 from RPCI and 34 from the literature)

Characteristics	
Age at diagnosis of MDS, median (range)	59.2 (16–82)
Age at diagnosis of AD, median (range)	58.8 (16–82)
Male gender, n (%)	31 (70)
Synchronous, n (%)	25 (56)
MDS pathology	
RA, n (%)	16 (36)
RAEB-1 and 2, n (%)	15 (34)
RARS, n (%)	6 (14)
Other (MDS/MPN), n (%)	4 (9)
CMML, n (%)	3 (6)
Karyotype	
Normal, n (%)	21 (44)
≥2 abnormalities, n (%)	6 (13)
del(5q) (sole), n (%)	5 (11)
del(20q), n (%)	4 (9)
Trisomy 8, n (%)	3 (6)
N/A, n (%)	9 (20)
AD Characteristics	
Vasculitis, n (%)	12 (27)
Seronegative arthritis, n (%)	8 (18)
Skin lesions, (Sweet, pyoderma and ictyosis) n (%) Relapsing polychondritis, n (%)	6 (13)
Pulmonary, n (%)	4 (9)
GI (Colitis and pancreatitis), n (%) Thyroiditis, n(%)	4 (9)
Hemolytic anemia with DAT, n (%)	3 (7)
Other[a] n (%)	3 (7)
	3 (7)
	15 (31)
Treatment of MDS	
Hypomethylating agents, n (%)	13 (29)
Other, n (%)	9 (20)
None, n (%)	8 (18)
N/A, n (%)	6 (13)
Low-dose cytarabine, n (%)	4 (9)
Transfusion only, n (%)	4 (9)
Treatment of AD	
Prednisone alone, n (%)	21 (47)
Prednisone and additional drugs, n (%)	11 (25)

Characteristics	
Other, n (%)	6 (13)
None, n (%)	4 (9)
N/A, n (%)	2 (4)
Outcome of AD	
Improvement of AD, n (%)[b]	31 (70)
Worsening, n (%)	8 (18)
N/A, n (%)	5 (11)
Outcome of MDS	
Persistent, n (%)	17 (38)
Transformation to AML, n (%)	11 (25)
Improvement of MDS, n (%)	8 (18)
N/A, n (%)	8 (18)

Two cases of rheumatoid arthritis, ITP, nephritis, Sjogren's and myositis each.

One case of PMR, SLE, Uveitis, positive rheumatoid factor and ANA associated with athralgias each.

Abbreviations: AD, autoimmune diseases; AML, acute myeloid leukemia; ANA, antinuclear antibodies; CMML, chronic myelomonocytic leukemia; DAT, direct antiglobulin test; del, deletion; Gl, gastrointestinal; ITP, idiopathic thrombocytopenic purpura; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasm; n, number; N/A, not available; PMR, polymyalgia rheumatica; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; SLE, systemic lupus erythematous;

[a]Only AD manifestations >5% are presented, less frequent diseases included:

[b]Only described in patients who received treatment for AD

Table 5

List of the frequencies of abnormal laboratory autoimmune findings from 44 cases reported (including 10 from our institute):

Test resul[a]	Number of cases with abnormal results/Number of case tested (%)
Elevated ESR	15/17 (88%)
Elevated CRP	11/14 (78%)
DAT	5/15 (33%)
RF	4/15 (26%)
ANA	5/23 (21%)
Anti DsDNA	1/7 (14%)

Less frequent presentations include:

Two cases with anti-platelets antibodies.

Abbreviations: ANA, antinuclear antibodies; Anti DsDNA, double stranded DNA antibodies; CRP, C reactive protein; DAT, direct antiglobulin test; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor;

[a]Only presentations >5% are presented.