

# Myelodysplastic Syndrome and Autoimmune Disorders: Causal Relationship or Coincidence?

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## Abstract

Myelodysplastic syndromes are heterogeneous group of clonal hematologic malignancies characterized by peripheral blood cytopenias secondary to the ineffective hematopoiesis. ADs are frequently reported in MDS, the incidence ranging from 10 to 30%, and particularly ADs are more frequently seen at CMML. ADs may prone patient to MDS, especially when immune suppressors such as azathioprine are used for the underlying AD. Both innate and adaptive immune systems, and different cytokines including interleukins, TNF- $\alpha$ , and C-X-C motif chemokine 10 (CXCL10) contribute in immune dysregulation of MDS. Vasculitis, seronegative rheumatoid arthritis, SLE, Behçet's disease, RP, and AIHA are just some of the ADs occurring concomitantly with MDS. Although hematopoietic growth factors are recommended by the American Society of Clinical Oncology (ASCO), it has been recognized from several case reports that treatment of the underlying MDS may resolve the associated autoimmune disorders. The heterogeneity and complexity of pathology, clinical manifestations, response to therapy, and prognosis of MDS and its immune dysregulation make the prognosis of MDS with autoimmune diseases a matter of debate. Better understanding of the immune dysregulation of MDS in the molecular level may help to design prospective, double blind clinical trials to find the best treatment options for autoimmune disorders associated with MDS.

**Keywords:** autoimmune disorders (ADs), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), Behçet's disease, systemic lupus erythematosus (SLE), azathioprine, azacitidine, tumor necrosis factor alpha (TNF- $\alpha$ ), regulatory T-cells (Treg), autoimmune hemolytic anemia (AIHA), vasculitis, chronic inflammatory demyelinating polyneuropathy (CIDP), neutrophilic dermatosis, Henoch-Schonlein purpura, relapsing polychondritis (RP), granulomatosis with polyangiitis (GPA), giant cell arteritis (GCA), polyarteritis nodosa (PAN)

## 1. Introduction

Myelodysplastic syndromes (MDS) are characterized by peripheral blood cytopenias secondary to the ineffective hematopoiesis, and represent a heterogeneous group of clonal hematologic malignancies in which abnormal multipotent progenitor cells are involved. As a result, there is an increased risk of bleeding diathesis and anemia requiring frequent transfusions, infections, and progression to

acute myeloid leukemia [1–4]. It is a very well-known fact that a large spectrum of genetic mutations is involved in MDS pathogenesis that may affect clinical outcome and response to the treatment. These genetic mutations may control cell cycle by affecting key proteins of spliceosome, DNA repair, kinase signaling, tumor suppressor genes, and transcription factors, changing bone marrow micro environment, resulting in hypercellular bone marrow with peripheral cytopenias through enhanced programmed cell death (PCD) and bone marrow dysfunction [5, 6]. To overcome programmed cell death, hematopoietic growth factors such as erythropoiesis stimulating agents (ESAs) and granulocyte colony stimulating factor (G-CSF) are the 1st step in management of the low-grade MDS recommended by the American Society of Clinical Oncology (ASCO) to reduce early apoptosis [1].

Thrombopoietic stimulating agents (TSAs), ESAs, G-CSF, antithymocyte globulin (ATG) [7], lenalidomide [8], and hypomethylating agents are some of the non-transplantation options for management of the MDS patients suggesting that immune dysregulation plays a pivotal role in MDS pathogenesis [1]. Although its etiology is not clear, it has been shown that natural killer (NK) cell activity and its response to chemokines is decreased in MDS, and natural killer cells will be progressively more dysfunctional with MDS progression [9]. It has been shown that although dysfunctional regulatory T-cells (Treg), cells in charge of suppressing T helper (Th) activity, contribute in early stages of MDS, Th expands in the later stages of MDS, and there function is significantly reduced with treatment [10].

Tumor necrosis factor alpha (TNF- $\alpha$ ) level is higher in bone marrow and peripheral blood plasma of MDS patients, and may reflect an unfavorable outcome [11, 12]. Study shows that plasma level of 19 cytokines are significantly altered compared with normal individuals, among all of them, C-X-C motif chemokine 10 (CXCL10) and interleukin 6 were associated with shortened survival [13]. The relationship between shorter survival and interleukin 6 levels is very well known, and high producing genotypes of both TNF- $\alpha$  and interleukin 6 are highly associated with transfusion dependency for both anemia and thrombocytopenia, and severity of the bicytopenias [14]. Interferon regulatory factor-1 (IRF-1), a transcriptional activator of interferon system, has anti oncogenic properties, inhibits tumor formation, and regulates innate immune response. It has been shown that IRF-1 mRNA is 10 fold decreased in MDS patients, while it is increased in MDS patients with autoimmune disorders, showing that IRF-1 may promote inflammation and autoimmunity and has a protective roll in MDS patient's [15].

Although it has been reported that MDS is significantly associated with autoimmune disorders, it may occur secondary to the autoimmune disorders per se [16] or exposure to the therapeutic agents used for treatment of autoimmune disorders. A retrospective study in Sweden on 1662 MDS patients and 42,878 matched controls revealed that underlying autoimmune disorder increased risk of MDS by 2.1 with highest risks observed with prior autoimmune hemolytic anemia (AIHA), polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA), giant cell arteritis (GCA) and aplastic anemia. It was speculated that chronic stimulation of the immune system may act as a trigger and prone the patient to MDS [17]. In a retrospective study of 2471 patients, it was found that MDS occurred subsequent to autoimmune disorders, most commonly rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, polyarteritis nodosa, discoid lupus erythematosus, and pernicious anemia were associated with MDS [18]. In a case control study of 80 for MDS patients, it was found that there is strong and statistically significant evidence that MDS occurred after autoimmune disorders with Grave's disease and Hashimoto's thyroiditis were among the most important disorders [19]. There is a case report of limited granulomatosis with polyangiitis (GPA) treated with corticosteroids, who did develop myelodysplastic syndrome, papillary thyroid carcinoma, and gastric adenocarcinoma [20].

There are several reports regarding therapy related MDS in population with autoimmune disorders who underwent disease modifying antirheumatic drugs (DMARDs) therapy. In a retrospective case-control study of 40,011 patients with 27 kinds of autoimmune disorders, 311 patients met the inclusion criteria, 86 of them had MDS, and found azathioprine exposure has increased 7 fold myeloid neoplasms in a median of 8 years. In this study, methotrexate, and mycophenolate mofetil did not elevate the risk of myeloid neoplasms [21]. However, there is a case report regarding association of low-dose oral methotrexate therapy with MDS in a rheumatoid arthritis patient [22]. In another study, from 370 rheumatologic patients who received azathioprine for at least 1 year, 59 patients underwent bone marrow examination and 2 of them found to have MDS. This study revealed that risk of secondary MDS is 100 fold higher in patients who received azathioprine for their rheumatologic disorders. Chromosomal examination of the patients with MDS secondary to the azathioprine showed abnormalities of chromosome 7 in majority of them (8 out of 10) [23]. There is also evidence that MDS patients who have autoimmune disorders might respond to hypomethylating agents such as azacitidine and decitabine [24].

## **2. Rheumatologic manifestations of MDS**

It is a very well-known fact that about 10–30% of MDS patients may present with a variety of autoimmune or laboratory manifestations or develop an autoimmune disorder. These manifestations are polymorphic and include leukocytoclastic vasculitis, clubbing, peripheral neuropathy, autoimmune hemolytic anemia, polyarthritis, myositis, acute or systemic vasculitis, Raynaud's phenomenon, polyarteritis nodosa, vitiligo, iritis, colonic ulcerations, pulmonary involvement, and reported autoimmune disorders include rheumatoid arthritis, Sjogren's disease, giant cell arteritis, polymyalgia rheumatica, relapsing polychondritis, Behçet's disease, and systemic lupus erythematosus. Although autoimmune manifestations are mostly seen during the course of MDS, autoimmune disorders may occur before MDS diagnosis. Laboratory manifestations of MDS include hypergammaglobulinemia, hypogammaglobulinemia, monoclonal gammopathy, positive direct antiglobulin test (DAT), positive ANA, rheumatoid factor, cryoglobulinemia, and anti-double-stranded DNA.

## **3. Autoimmune disorders in myelodysplastic syndrome**

Several studies support that autoimmune disorders may occur in the setting of MDS, and treating MDS with immunosuppressors may improve the autoimmune disorder. Although there were several case reports of MDS preceding autoimmune disorders, the first comprehensive retrospective study in 1986 on 104 MDS patients revealed two patients had pernicious anemia, two had hypothyroidism, and one had both pernicious anemia and hypothyroidism [23]. Later, in a retrospective study in 1994, five patients with MDS reviewed and revealed polyarthritis with positive rheumatoid factor (RF) and necrotizing vasculitis [25]. In another retrospective study in 1995, 221 patients with MDS reviewed and found 30 patients with autoimmune disorders, and categorized patient to three categories of acute systemic vasculitis or autoimmune disorder, chronic or isolated autoimmune phenomena, and classic connective tissue disorders. Skin vasculitis, arthritis, and fever were among the most common autoimmune manifestations [26].

A case series in 2002 showed various autoimmune paraneoplastic disorders including vasculitis, pyoderma gangrenosum, Coombs negative autoimmune

hemolytic anemia, autoimmune thrombocytopenia, and chronic inflammatory demyelinating polyneuropathy (CIDP) with good response to immunosuppressive therapy [27]. In a retrospective review of 235 MDS patients autoimmune manifestations such as skin vasculitis (24%), noninfectious fever (13%), arthralgia and arthritis (13%), peripheral neuropathy (10%), and pulmonary infiltrates (8%) were more common than systemic vasculitis [28]. In a cohort of 1408 patients with MDS, 391 (28%) had autoimmune disorders, with hypothyroidism (44%), as the most prevalent, and idiopathic thrombocytopenic purpura (12%), rheumatoid arthritis (10%), and psoriasis (7%) were among the common manifestations of autoimmune diseases [29].

In a retrospective study of 67 MDS patients with autoimmune diseases, neutrophilic dermatosis was the most common autoimmune disease (35.8%), followed by Behçet's disease (14.9%), and rheumatoid arthritis (13.4%) [30].

### **3.1 Vasculitis**

The association between MDS and vasculitis is rare, but more common than solid tumors, and has been described for decades. Cutaneous vasculitis presents by palpable purpura mainly in lower extremities that involves small vessels and is characterized by perivascular inflammation and vessel wall damage by infiltrating neutrophils. Although both cutaneous and systemic vasculitis has been reported in MDS patients, at times they can be seen together in MDS patients. For instance, in a case series of 6 biopsy proven cutaneous vasculitis patients with MDS, 3 patients had evidence of systemic vasculitis [31]. In one case, MDS patient with biopsy proven cutaneous vasculitis developed acute myeloid leukemia within 4 months of vasculitis diagnosis [32]. Henoch-Schonlein purpura, a small vessel vasculitis with IgA dominant immune deposits has been described in MDS patients [33].

The association of MDS and polyarteritis nodosa (PAN) type medium-vessel vasculitis has been reported [34]. In a retrospective study of 8 patients with chronic myelomonocytic leukemia (CMML), with vasculitis involved the medium-vessel, fulfilling the criteria for classic PAN, the presentation was non-specific, and patients developed atypical manifestations [35]. There is a case report of 43-year-old man who qualified for a diagnosis of PAN and developed systemic vasculitis at the time of chronic myelomonocytic leukemia (CMML) diagnosis [36]. There is a report of two cases with CMML who presented with PAN-like systemic vasculitis with bilateral perirenal hemorrhage and negative antineutrophil cytoplasmic antibody with improvement of vasculitis with systemic steroids [37].

Although most MDS associated vasculitis described as leukocytoclastic vasculitis, published case reports documented large vessel vasculitis as autoimmune complication of MDS. Aortitis has been reported as an autoimmune manifestation of an MDS patient at presentation [38]. There is a report of two MDS cases that presented with acute large vessel vasculitis with rapid improvement with systemic steroids [39]. In a retrospective analysis of 271 temporal arteritis patients, it was found that 20 patients had malignancy, of which 11 patients had MDS, favoring a relationship between large vessel vasculitis and MDS [40]. There is a case report of Takayasu's arteritis diagnosed shortly after diagnosis of MDS, with progression to AML regardless of improvement of vasculitis with immunosuppressive treatment [41]. There is a case report of a 71-year-old woman presenting with fever, neck pain, anemia, and thrombocytopenia, with positive positron emission tomography (PET)/CT scan of the aorta and carotid arteries with negative temporal artery biopsy who received the diagnosis of MDS after a bone marrow aspiration analysis [42, 43].



### **3.2 Behçet's disease**

A multisystem, chronic inflammatory disease of unknown etiology, Behçet's disease (BD) is characterized by recurrent oral and genital ulcers, uveitis, arthritis, and vascular involvement of several organs including pulmonary, central nervous system and gastrointestinal tract. In a retrospective study of 805 BD patients, 16 patients had MDS, from which 43.8% had BD prior to MDS, 18.7% diagnosed after MDS and 37.5% had concurrent BD and MDS. It has been shown that trisomy 8 has been accumulated in all of BD patients with MDS, and these patients more likely to be female, older age, and have fever and ileocecal ulcerations [44]. In a retrospective study of 46 MDS patients, 8 patients had trisomy 8, 5 of them had multiple intestinal ulcers, a common feature of BD. Two of the MDS patients with trisomy 8 and multiple intestinal ulcers were treated with granulocyte-colony stimulating factor (G-CSF), aggravating their symptoms, suggesting G-CSF should be used cautiously in this subgroup of MDS patients [45]. There is several case reports of BD associated with MDS [46–49]. In a case report of two patients with BD and MDS, it has been suggested that PET/CT may help diagnosis of both BD and MDS with high uptake by bone marrow in MDS patients and genital and gastrointestinal aphthous ulcers in BD patients [50]. It has been suggested that the frequency of gastrointestinal involvement is more common in MDS-associated BD patients than general BD population [51].

### **3.3 Inflammatory arthritis**

There are several case reports and small series of inflammatory arthritis and MDS co-occurrence. In a retrospective study of 28 MDS patients, 8 had acute seronegative inflammatory arthritis with good response of arthritis to steroids [52]. In a French multicenter retrospective study of 22 patients with MDS, 77% of patients had polyarthritis, and 68% had symmetric joint involvement. Radiologic erosions are rare, and MDS associated arthritis is more frequent in refractory anemia with excess blast (RAEB) [53].

### **3.4 Miscellaneous**

There are several case reports of relapsing polychondritis (RP) presenting as a paraneoplastic disorder in the setting of MDS [54, 55]. In a retrospective study of hematological changes in 19 patients with relapsing polychondritis, MDS was found in three RP patients [56]. Autoimmune hemolytic anemia has been reported in association with MDS [57–59]. Association of systemic lupus erythematosus and MDS has been reported [60–62].

### **3.5 Immunological abnormalities**

It is a very well-known fact that a spectrum of immunological abnormalities occur in MDS. In a retrospective study of 104 MDS patients, 12.5% had monoclonal gammopathy, 19% had low immunoglobulin levels, 32% had polyclonal rise in serum immunoglobulin level, and 8.1% had positive direct antiglobulin test (DAT) [25]. In a case series of 142 patients with MDS and CMML, 23.2% had non-organ specific autoantibody ANA as the most frequent serologic finding [25]. Thrombocytopenia is a common finding in MDS, and can be seen in up to two third of the patients. In a study of 54 MDS patients with no treatment of transfusions, direct platelet immunofluorescence test for platelet associated IgG was positive in 28 patients. Patients with higher amount of platelet associated IgG, had significantly higher mean platelet volume (MPV), thrombocytopenia and worse outcome [63].

## **4. Prognosis**

It has been suggested that appearance of skin vasculitis in MDS patients may reflect acute myeloid leukemia transformation. In a prospective study of 157 MDS patients for a median of 44 months, 15 patients (9.55%) experienced skin lesions, and neutrophilic dermatosis (7, 4.46%), specific lesions (5, 3.18%), cutaneous vasculitis (2, 1.27%) and Behçet's disease (1, 0.63%) were reported. This study revealed that neutrophilic dermatosis was more prevalent in MDS patients, may confer the higher risk of acute myeloid leukemia transformation [64]. In another study of 84 newly diagnosed MDS patients, correlation of cutaneous findings with immunologic parameters and prognostic features of MDS examined, and revealed that 21 patients had skin lesions at presentation, and skin manifestations were a significant predictor of the high-risk MDS subgroup [65].

In a retrospective study of 153 MDS patients, 12% had autoimmune diseases, and 63% has at least one immunological abnormality in test results. In this study, the survival of patients without autoimmune diseases was better than patients with autoimmune disease [66]. However, in a 4 year prospective study of 70 MDS patients, 53 patients without and 13 patients with autoimmune disease, there was no particular difference concerning prognosis between two groups. And patients with autoimmune diseases were not statistically different in survival compared with MDS patients without autoimmune disease [67].

## **5. Treatment**

Autoimmune disorders associated with MDS may predate or occur after MDS diagnosis, and their treatment many be associated with significant side effects in MDS patients. It has been recognized from several case reports that treatment of the underlying MDS may resolve the associated autoimmune disorders. In a transfusion dependent MDS patient who was receiving G-CSF and erythropoietin, neutrophilic dermatosis did not improve with G-CSF withholding. Two months after starting 5-azacitidine, a hypomethylating agent, the skin rash completely resolved, and did not recur after 2 years [68]. In another case series of 3 MDS patients with autoimmune disorders, 5-azacitidine improved both MDS and autoimmune disorders although long term steroid could not be tapered [69].

In a retrospective study of 123 MDS patients with autoimmune disorders, 118 patients (96%) were treated with steroids, and 48% of patients were required a second line treatment for refractory disease or relapse. Although autoimmune disorder treatment did not improve MDS, MDS treatment with 5-azacitidine improved the autoimmune disorder in 9 out of 11 (80%) of patients [70]. In another retrospective study of 123 MDS/CMML patients with autoimmune disorders, 28 patients received at least 5 cycles of azacitidine, 20 of them did not respond to steroids. In 86% of MDS/CMML patients, clinical autoimmune syndromes improved by azacitidine, and prednisone dose tapered in 64% of patients [71].

The overall effect of biologic medications efficacy in MDS patients who presented with autoimmune disorder is not clear. As of today, there is only one retrospective study of MDS patients with autoimmune disorders and biologic medications. In this study of at least one biologic medication, 29 patients followed for at least 3 years. 89% of patients received a biologic after failure or intolerance of two disease modifying anti rheumatic agents (DMARDs), however, 11% of patients received biologics as a first line treatment. Except rituximab, a CD-20 blocker, mainly for vasculitis (58% response), there was partial or insufficient response to

TNF- $\alpha$  antagonists, and their efficacy is much less in autoimmune disorders associated with MDS than autoimmune disorders without MDS. Overall, response rate to 5-azacitidine in MDS-associated autoimmune disorders was 67% in favor of a causality relationship between MDS and autoimmune disorders [72].

## 6. Conclusion

Myelodysplastic syndromes are a heterogeneous group of progressive clonal hematopoietic stem cell disorders characterized by a varying degree of peripheral cytopenia, and increased probability of transformation to acute myeloid leukemia. MDS and particularly CMML are frequently associated with a variety of autoimmune disorders that can be diagnosed concomitantly with MDS or before or after MDS. The heterogeneity and complexity of pathology, clinical manifestations, response to therapy, and prognosis of MDS and its immune dysregulation makes the prognosis of MDS with autoimmune diseases a matter of debate. Prospective, randomized studies are required to confirm the autoimmune diseases role in MDS prognosis.

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## Disclosure

None.

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