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Myelodysplastic syndromes and autoimmune diseases—Case series and review of literature

Omar Al Ustwani[a], Laurie A. Ford[a], Sheila J.N. Sait[b], Anne Marie W. Block[b], Maurice Barcos[c], Carlos E. Vigil[a], Elizabeth A. Griffiths[a], James E. Thompson[a], Eunice S. Wang[a], Julian Ambrus Jr.[d], Meir Wetzler[a,*]

[a] Leukemia Section, Department of Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo NY, USA
[b] Clinical Cytogenetics Laboratory, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo NY, USA
[c] Department of Pathology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo NY, USA
[d] Department of Medicine, State University of New York, Buffalo General Hospital, Buffalo, NY, USA

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ABSTRACT

Our objective was to recognize the association of autoimmune diseases (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.

1. 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.

2. 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), anti-nuclear antibody (ANA), complement 3 (C3), 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.

3. Results

3.1. Patient characteristics

As shown in Tables 1 and 2, ten large series [3–12] encompassing a total of 2466 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.

* Corresponding author at: Leukemia Section, Department of Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA. Tel.: +1 716 845 8447; fax: +1 716 845 2343.
E-mail address: meir.wetzler@roswellpark.org (M. Wetzler).

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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, Pannniculitis (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.

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 and 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.

3.2. 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.

3.3. 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 and del(5q) (10%) were less common (data not shown) [38]. 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.

3.4. 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