Autoimmune Hemolytic Anemia with Myelodysplastic Syndrome

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Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal cell disorders characterized by ineffective hematopoiesis manifested by one or more cytopenias.[1] The incidence is higher in men, and is about 3-4 individuals per 100,000 in the United States and may exceed 20/ 100,000 persons after the age of 70 years.[2] Risk factors for development of MDS include prior chemotherapy, radiation therapy, smoking, and exposure to benzene. The most common cytogenetic alteration in MDS is a deletion of the short arm of chromosome 5. We report a patient with an isolated trisomy 21, which constitutes about 1.1-2.2 % of the total cytogenetic alterations in MDS.[3,4] To our knowledge, this is the first reported case of autoimmune hemolytic anemia (AIHA) and MDS with isolated trisomy 21.

Case Report

A 62-year-old Caucasian male was initially admitted for generalized weakness and fatigue. The symptoms started three months prior to presentation at the referring hospital. The patient reported anorexia, weight loss, and exercise intolerance. He denied any bleeding symptoms to suggest infection. On admission to our hospital, his vital signs were within normal limits. His physical exam showed pallor, but otherwise was unremarkable.

Initial labs are summarized in Table 1. His peripheral smear showed 65% neutrophils, 9% bands, 9% blasts, 2% metamyelocytes, and 1% myelocytes. He underwent a bone marrow biopsy, which was consistent with myelodysplastic syndrome (RAEB-1). His cytogenetics showed trisomy 21 as the sole abnormality. Testing for vitamin B_{12} and folic acid were unremarkable. The patient was diagnosed with AIHA and treatment was started with prednisone at 1 mg/kg.

The patient's hemoglobin improved with prednisone. The prednisone was tapered over two months and his Coombs testing became negative shortly after the course. The patient's platelet count continued to deteriorate and treatment was initiated with the hypomethylating agent, decitabine. The patient tolerated this treatment well and had improvement in his cytopenia. His course was complicated by gastrointestinal bleeding and a pneumonic infection. The patient died from complications of an empyema.

Discussion

This case illustrates a commonly overlooked association between two different hematologic diseases, myelo-dysplastic syndrome and autoimmune hemolytic anemia. Our patient had evidence of intravascular hemolysis, manifested by his reticulocytosis, high LDH and bilirubin,

Table 1. Initial labs obtained on admission.

Lab	Hb (g/dL)	WBC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	MCV (mm^3)	Reticulocyte count
Values	10.5	24.2	37	99	9.3%

Lab	LDH (IU/L)	Haptoglobin (mg/dL)	Bilirubin (mg/dL)	Coombs test
Values	568	3	2.8	Positive

and low haptoglobin. There was evidence of autoimmunity with the Coombs test positive for pan agglutinating IgG. This improved with standard first line treatment. The bone marrow biopsy result was consistent with myelodysplastic syndrome, refractory anemia with excess blasts (RAEB-1 with 7% blasts in the bone marrow).

Autoimmune hemolytic anemia is due to the immunologic destruction of red blood cells mediated by autoantibodies directed against red blood cells antigens.[5] The antibodies can be of "warm" or "cold" subtype. The majority of warm agglutinins are IgG subclass antibodies. They react to antigens at body temperature in contrast to cold agglutinins which are mostly IgM subclass, and react to RBC antigens at a temperature lower than the body's core temperature. The diagnosis usually is made with the finding of an elevated reticulocyte count, increased lactate dehydrogenase, and indirect bilirubin in the setting of a positive direct Coombs test (direct antiglobulin test).

There is increasing evidence that autoimmunity plays an important role in myelodysplastic syndromes. Autoimmune manifestations (AIM) are more common than thought in the setting of MDS. Their frequency ranges from 10-18.5% of patients with MDS.[6,7] These manifestations can be classified into five classes:[4]

1) Acute systemic vasculitis or autoimmune disorder.
2) Chronic or isolated autoimmune phenomena.
3) Classical connective tissue disorders.
4) Immune-mediated hematological abnormalities.
5) Asymptomatic serological immunologic abnormalities.

The association of AIM and MDS was first described in 1982 as AIHA one year after the diagnosis of MDS.[6] Subsequently, multiple cases and studies have been published emphasizing the relationship between autoimmunity and MDS.

In a study by Sokol et al.,[8] 15 of 46 patients with MDS had clinically important autoimmune hemolysis. Pendry et al.[9] reported a case of MDS presenting as AIHA. The first pediatric case was reported by Ören et al.[10] The improvement of both disorders was noticed with mycophenolate mofetil.[11] João et al.[12] and Terpos et al.[13] described two cases of MDS, AIHA, and non-Hodgkin's lymphoma. Giagounidis et al.[14] reported a case of AIHA and a case of autoimmune arthritis in association with MDS with 5q deletion. Pilorge et al.[15] reported three cases of AIM and MDS with improvement with 5-azacitidine.

The pathogenesis of the association of these two disorders is still unclear. Current hypotheses relate development of autoimmune hemolytic anemia to dysregulated immunity. In a study by Barcellini et al.,[16] 53.8% of patients showed autoimmune

phenomena to erythroblasts in the bone marrow, but none in the peripheral blood.[14,16]

AIHA in MDS may be underdiagnosed for several reasons including the assumption that anemia is due to MDS.[14] Besides, Coombs-negative hemolytic anemia can be masked by reticulocytopenia caused by MDS.

It is unclear if autoimmune manifestations carry any prognostic implications to the diagnosis of MDS. In a study by Enright et al.,[17] patients with the combination of the two disorders were younger, more often had MDS related to prior chemotherapy, and had additional cytogenetic abnormalities. The onset of AIM was associated with clinical deterioration, as the median survival after AIM diagnosis was only nine months compared to 25 months after MDS diagnosis. In addition, the initial response to steroids carried a better prognosis.

Conclusion

Autoimmune hemolytic anemia is a rare, but commonly overlooked cause of anemia in patients with myelodysplastic syndrome. Further reports may delineate the association of autoimmune manifestations and MDS better and its potential prognostic and therapeutic implications. A link may be found between chromosomal abnormalities and their concomitant incidence.

References

1 Barzi A, Sekeres MA. Myelodysplastic syndromes: A practical approach to diagnosis and treatment. Cleve Clin J Med 2010; 77(1):37-44. PMID: 20048026.

2 Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. Blood 2008; 112(1):45-52. PMID: 18443215.

3 Haase D. Cytogenetic features in myelodysplastic syndromes. Ann Hematol 2008; 87(7):515-526. PMID: 18414863.

4 Haase D, Germing U, Schanz J, et al. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: Evidence from a core dataset of 2124 patients. Blood 2007; 110(13):4385-4395. PMID: 17726160.

5 Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine. 18th edition. New York: McGraw-Hill, 2012. ISBN: 007174889X.

6 Saif MW, Hopkins JL, Gore SD. Autoimmune phenomena in patients with myelodysplastic syndromes and chronic myelomonocytic leukemia. Leuk Lymphoma 2002; 43(11):2083-2092. PMID: 12533032.

7 Giannouli S,Voulgarelis M, Zintzaras E, Tzioufas AG, Moutsopoulos HM. Autoimmune phenomena in myelodysplastic syndromes: A 4-yr prospective study. Rheumatology (Oxford) 2004; 43(5):626-632. PMID: 14983106.

8 Sokol RJ, Hewitt S, Booker DJ. Erythrocyte autoantibodies, autoimmune haemolysis, and myelodysplastic syndromes. J Clin Pathol 1989; 42(10): 1088-1091. PMID: 2584409.

9 Pendry K, Harrison C, Geary CG. Myelodysplasia presenting as autoimmune haemolytic anaemia. Br J Haematol 1991; 79(1):133-134. PMID: 1654992.

10 Oren H, Ucar C, Gülen H, Duman M, Irken G. Autoimmune hemolytic anemia occurring with myelodysplastic syndrome: Report of a pediatric case and review of the literature. Ann Hematol 2001; 80(9):540-542. PMID: 11669304.

11 Lin JT, Wang WS, Yen CC, et al. Myelodysplastic syndrome complicated by

autoimmune hemolytic anemia: Remission of refractory anemia following mycophenolate mofetil. Ann Hematol 2002; 81(12):723-726. PMID: 12483369.

[12] João M, Silva N, Lucas M, et al. Long lasting myelodysplastic syndrome complicated by autoimmune hemolytic anemia and non-Hodgkin's lymphoma. Eur J Haematol 2002; 68(2):122-124. PMID: 11982620.

[13] Terpos E, Theocharis S, Panitsas F, Philippidis T, Kotronis E, Karkantaris C. Autoimmune hemolytic anemia with myelodysplastic features followed by bilateral adrenal non-hodgkin lymphoma: A case report and review of the literature. Leuk Lymphoma 2004; 45(11):2333-2338. PMID: 15512826.

[14] Giagounidis AA, Haase S, Germing U, Heinsch M, Aul C. Autoimmune disorders in two patients with myelodysplastic syndrome and 5q deletion. Acta Haematol 2005; 113(2):146-149. PMID: 15802895.

[15] Pilorge S, Doleris LM, Dreyfus F, Park S. The autoimmune manifestations associated with myelodysplastic syndrome respond to 5-azacytidine: A report on three cases. Br J Haematol 2011; 153(5): 664-665. PMID: 21275970.

[16] Barcellini W, Zaninoni A, Imperiali FG, et al. Anti-erythroblast autoimmunity in early myelodysplastic syndromes. Haematologica 2007; 92(1):19-26. PMID: 17229631.

[17] Enright H, Jacob HS, Vercellotti G, Howe R, Belzer M, Miller W. Paraneoplastic autoimmune phenomena in patients with myelodysplastic syndromes: Response to immunosuppressive therapy. Br J Haematol 1995; 91(2):403-408. PMID: 8547082.

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