

ASSOCIATION OF MYELODYSPLASTIC SYNDROME AND AUTOIMMUNE DISORDERS IN NORTH KERALA

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ABSTRACT

BACKGROUND

Autoimmune phenomenon is described in many cases of myelodysplastic syndrome. The incidence of autoimmune phenomenon in de novo cases of myelodysplastic syndrome varies from 10 to 30 percent of cases in Western literature with arthritis, vasculitis or haemolytic anaemia. The data from India is very scanty and that from Kerala, virtually non-existent.

The aim of this study is to evaluate the prevalence of autoimmune phenomenon in diagnosed cases of myelodysplastic syndrome focusing on the prevalence of the different types of autoimmune phenomenon in the cases of myelodysplastic syndrome and to examine if any subtype of myelodysplastic syndrome is more associated with autoimmune phenomenon.

MATERIALS AND METHODS

For this purpose, we studied 117 consecutive confirmed cases of myelodysplastic syndrome that presented to the department of Medicine and Haematology in Calicut Government Medical College between July 2009 and June 2013. The statistical incidence and behaviour of the different autoimmune phenomenon was studied using Chi square test and compared with the existing data.

RESULTS AND CONCLUSIONS

The prevalence of autoimmune disorders in the study population of myelodysplastic syndrome was very high compared to western studies (44.44%). There was no gender predilection for the autoimmune phenomenon. Of this the most common autoimmune disease that occurred was autoimmune haemolytic anaemia followed by arthritis. There was no increased incidence of autoimmune phenomenon in any specific subtype of MDS. There was no alteration statistically between myelodysplastic syndrome patients who had autoimmune phenomenon to that of patients who did not, regarding haemoglobin levels, ESR values, incidence of complications and transformation to acute leukaemia.

KEYWORDS

Myelodysplastic Syndrome, Autoimmune Phenomenon.

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BACKGROUND

Myelodysplasia or Myelodysplastic syndromes are a heterogeneous group of hematologic disorders broadly characterized by cytopenias associated with a dysmorphic and usually cellular bone marrow, and consequent ineffective blood cell production. The various myelodysplastic syndromes are associated with a variety of autoimmune disorders, appearing either before or after the diagnosis of the disease. The incidence of autoimmune disorders described in literature varies from 10 to 30 percent of cases of myelodysplastic syndrome. Unfortunately, the data from India is very scanty and that from the state of Kerala is unavailable. The present study is aimed at

examining the prevalence of the various types of autoimmune disorders in the different subtypes of myelodysplastic syndrome in the population of North Kerala in India.

The objectives of this study were to study the prevalence of various autoimmune disorders in each of the subtypes of myelodysplastic syndromes and to investigate if there was any difference between the cases of myelodysplastic syndrome with and without autoimmune phenomenon with reference to the level of haemoglobin, ESR, the development of complications and the occurrence of Acute Myeloid Leukaemia.

MATERIALS AND METHODS

All clinically and histologically confirmed cases of myelodysplastic syndrome (MDS) diagnosed in the department of Medicine and Haematology, Calicut Govt. Medical College between July 2009 and June 2013 and followed up till December 2014. All age groups were included except paediatric (<13 yrs.). Patients were classified by World Health Organisation (WHO) classification and

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prognosticated. All clinical features were studied including autoimmune disorders along with it. Conditions pathologically simulating MDS like malnutrition, cyanocobalamin and folic acid deficiency, tuberculosis, toxin exposure, alcoholism, drug abuse, prior chemotherapeutic therapy, prior radiotherapy and HIV infection were ruled out by appropriate history and investigations. All patients were kept under follow up and subsequently developing clinical features with changes in blood count were observed. If abnormalities in blood count occurred, repeated peripheral smear and bone marrow examinations were performed. The statistical prevalence and behaviour of various types of autoimmune disorders in each of the subtypes of MDS was studied using Chi-square test and compared with the existing data.

Exclusion Criteria

Patients lost to follow up, whose pathological findings were not clear and patients aged less than 13 years were excluded.

OBSERVATIONS AND RESULTS

Of the 117 patients studied, 52 patients had autoimmune disorders (44.44%). Out of these, 28 patients were males and 24 patients were females. There was a total of 56 cases of autoimmune diseases in total with four patients developing multiple autoimmune diseases. Of this there were 11 cases (19.64%) of autoimmune haemolytic anaemia, 9 cases of (16.07%) seronegative arthritis, 8 cases (14.29%) of rheumatoid arthritis, 4 cases (7.14%) of immune thrombocytopenic purpura, 3 cases (5.36%) of psoriasis, autoimmune hepatitis, vitiligo, vasculitis and antral gastritis each. 2 cases (3.57%) of autoimmune hypothyroidism and aplastic anaemia each. There was 1 case (1.79%) of central retinal vein occlusion, antiphospholipid antibody syndrome, uveitis, retinitis pigmentosa and cortical vein thrombosis each (Figure 2). There were coexisting autoimmune disorders - rheumatoid arthritis and aplastic anaemia in a patient, vasculitis and vitiligo in a patient, ITP and autoimmune hypothyroidism in another patient and, rheumatoid arthritis and autoimmune haemolytic anaemia in another patient.

The number of patients having any autoimmune disorders in each type of myelodysplastic syndrome are 31.3% in RA(Refractory Anaemia), 0% in RARS (Refractory Anaemia with Ringed Sideroblasts), 57.9% in RCMD(Refractory Cytopenias With Multiline age Dysplasia), 50% in RAEB-1 (Refractory Anaemia with Excess Blasts-1), 46.7% In RAEB-2 (Refractory Anaemia with Excess Blasts-2), 25% in undifferentiated, 36.4% in CMML/MPD (Chronic Myelomonocytic Leukaemia/ Myeloproliferative Disorder) type and 50% in hypoplastic variants. The Chi square value was 0.343 which was not significant. (Figure-3)

93.9% patients who developed autoimmune phenomenon had anaemia defined by an average haemoglobin below 10g%, while 98.5% of patients without autoimmune phenomenon had laboratory evidence of anaemia. The difference was statistically not significant. (chi

square value was 0.233). 57.1% of patients with autoimmune phenomenon had and ESR above 100 mm/hr while 54.4% of patient without autoimmune phenomenon had an ESR of greater than 100 mm/hr. The difference was not statistically significant. (Chi square value was 0.449). 16.3% of patients with autoimmune phenomenon had developed acute myeloid leukaemia while 29.4% of patients without autoimmune phenomenon had developed acute myeloid leukaemia. The difference was not statistically significant. (chi square was 0.102). Death occurred in 28.6% of patient with autoimmune phenomenon while 25% of patient without autoimmune disease died. The difference was not statistically significant (0.66).

Total complication occurred in 63.3% of cases of patients with autoimmune diseases while it was present in only 50% of cases without autoimmune diseases. It was also not statistically significant. (chi square value of 0.154).

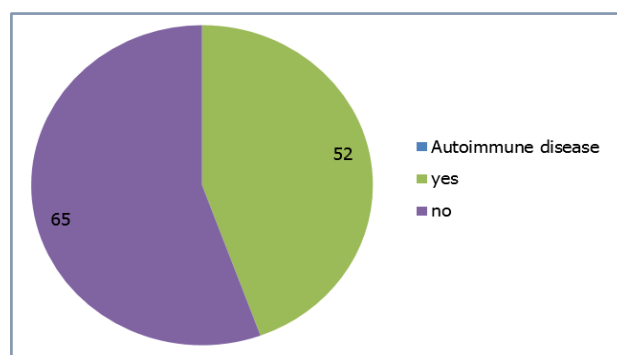


Figure 1. Figure Showing the Number of Patients with Autoimmune Disorders to the Total Number of Myelodysplastic Syndrome Patients

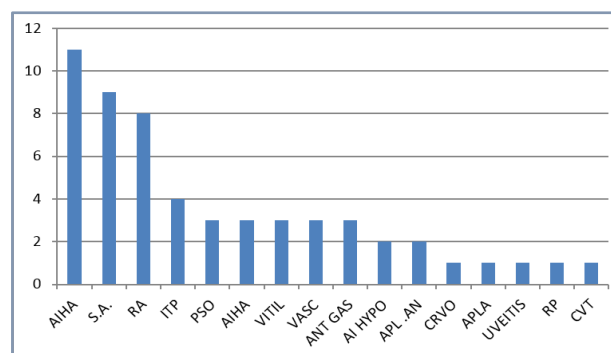


Figure 2. The Distribution of the Number of Cases (Y axis) to the Specific Types of Autoimmune Disorders (X axis)

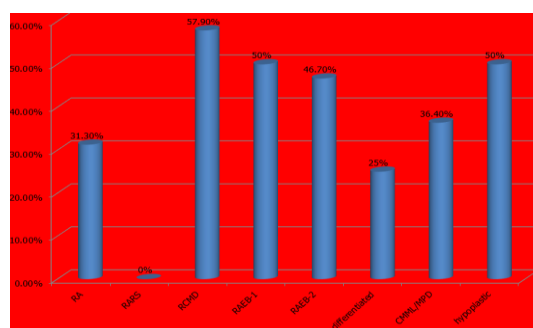


Figure 3. Distribution of the Percentage of Autoimmune Disorder in Each Type of Myelodysplastic Syndrome (Xaxis) Showing the Percentage of Autoimmune Disorders and Y axis the Subtype of MDS)

DISCUSSION

In the present study, there was a significant association between the prevalence of primary myelodysplastic syndrome and the prevalence of autoimmune disorders due to all the causes (found in 44.44% of patients). The most common autoimmune disorder found was autoimmune haemolytic anaemias. There was no statistical relationship between autoimmune disorders and any specific subtype of myelodysplastic syndrome.

All the autoimmune symptoms developed at least 3 months after the diagnosis of myelodysplasia. Our study population had showed a high frequency of autoimmune phenomenon. Autoimmune haemolytic anaemia was also high in our population. It also validates some of the observations that immunosuppressives and immunomodulators show benefit in treating myelodysplastic syndrome.¹

There was also no statistically significant association between the patients who had autoimmune phenomenon and those who had not regarding the level of haemoglobin, ESR value, progression to acute leukaemia, total complications or death.

A study by Amanda Wilson from Boston in 2009 found no evidence of autoimmune phenomenon in 87.9% of the patients.² The incidence of autoimmune phenomenon was not statistically significant. The inclusion criteria for the onset of autoimmune diseases was 2 years prior to the onset of MDS in this study. The commonest autoimmune disease was psoriasis followed by rheumatoid arthritis. Another study by Neelam Shah from Ahmedabad in 2009 showed 13.33% of the patients having features of autoimmune phenomenon with the majority having rheumatoid arthritis.³ Martin Stern from Italy had found in 2007 that there was significant association between MDS and autoimmune disorders like autoimmune haemolytic anaemias and immune thrombocytopenic purpura. 20% had also developed features of aplastic anaemia. Another study by Omer al Ustwad et al had found an incidence of 20% of patients with MDS developing autoimmune phenomenon.⁴ The most common was vasculitic syndromes (40%) followed by seronegative arthritis (27%) and neuropathy(24%). Another study by Saif MV and Hopkins JL had found 10% of MDS patients developing autoimmune phenomenon, with most common having vasculitis followed by arthritis.⁵ A study by Bouali F et al in 2005 found nearly 40% percent of patients with MDS developing autoimmune phenomenon.⁶ Thornston Braum in 2013 had found that nearly 30% of the patients had developed autoimmune diseases.⁷ The most common was polyarthritis (60%) followed by vasculitis. Enright et al had found the incidence of autoimmune phenomenon as 14 percent with vasculitis being the most common.¹ Another recent study of 1408 patients diagnosed with Myelodysplastic syndrome by Komrokji RS et al, 28 percentage of patients had autoimmune disorders, with hypothyroidism being the most common (44 percent).⁸ Other autoimmune disorders found were idiopathic thrombocytopenia purpura, rheumatoid arthritis, and psoriasis.^{9,10} Autoimmune disorders were most common in

female patients and those with RA and RCMD subtypes.^{11,8} Overall survival was more in patients with autoimmune disorders and transformation to AML was low in these patients.^{12,13} It was noted by Mekinian A, Grignano E et al from a French multicentric study published in 2016 that one third of patients had their autoimmune disorder diagnosed at the same time as their diagnosis of myelodysplastic syndrome and a third each before and after the diagnosis of myelodysplastic syndrome.¹⁴ The average duration in this study from the diagnosis of myelodysplastic syndrome to the appearance of autoimmunity was 8.4 months. A temporal association may suggest a common pathogenic pathway for both of these diseases.¹⁵ This study also found that majority of patients with MDS and autoimmune phenomenon were elderly males. These patients with autoimmune phenomenon are less associated with RARS subtype of MDS. Fain et al after studying 60 patients concluded that myelodysplastic syndrome was the most common cancer associated with autoimmune phenomenon.¹⁶ The most common autoimmune phenomenon he noted was vasculitis (equally distributed among leucocytoclastic and polyarteritis nodosa) was the most common autoimmune phenomenon in myelodysplastic syndrome. In most of the studies, laboratory abnormalities such as a positive antinuclear antibody, positive direct Coombs test and RA factor can be seen in many cases and their relationship to the future prognosis of the disease remain uncertain.^{11,10,12} As far as the prognosis of patients with MDS and autoimmune phenomenon are concerned, Okamoto et al has compared the prognosis of 19 patients of MDS with autoimmune phenomenon with that of MDS patients without autoimmunity and has found that outcome was inferior for these patients.¹⁷ But many recent studies have not demonstrated this relationship of associated autoimmune phenomenon and prognosis.

The association of immune dysregulation to MDS is being increasingly appreciated. A large variety of immune dysregulation is seen in MDS. How this association occurs or how they are related to each other remains to be unravelled. These autoimmune phenomenon occurring does not seem to confer worse survival although vasculitis has been shown to have a bad prognosis.^{13,14} As the study was done during the period of 2009 to 2013, the differentiation between the condition of CCUS (clonal cytopenias of undetermined significance) and MDS was not fully characterized. The relatively high incidence of autoimmunity in the present study may be due to the inclusion of autoimmune diseases manifesting as CCUS being included as undifferentiated MDS.

CONCLUSION

The prevalence of autoimmune disorders in the study population of myelodysplastic syndrome was very high compared to western studies. There was no gender predilection for the autoimmune phenomenon. Of this the most common autoimmune disease that occurred was autoimmune haemolytic anaemia followed by arthritis. There was no increased incidence of autoimmune phenomenon in

any specific type of MDS. There was no alteration statistically between MDS patients who had autoimmune phenomenon to that of patients who did not, regarding haemoglobin levels, ESR values, incidence of complications and transformation to acute leukaemia.

Limiting Factor of the Study

During the study, cytogenetic studies and genetic profiling of the patient was not done. IPSS score could not be applied due to the lack of cytogenetic studies. We found it useful to use low cost investigations available throughout the country even in primary care centers, to predict the course, complications and mortality rate of patients diagnosed with myelodysplastic syndrome developing autoimmune phenomenon.

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