Medical Science

25(118), December, 2021

The hidden truth about the development of myelodysplastic syndrome following immunosuppressant therapy for systemic sclerosis

Abishek Chakkravarthi M[1]✉, **Azeem I**[1], **Aswin Manikandan**[2], **Natarajan Suresh**[3]

To Cite:
Chakkravarthi AM, Azeem I, Manikandan A, Suresh N. The hidden truth about the development of myelodysplastic syndrome following immunosuppressant therapy for systemic sclerosis. Medical Science, 2021, 25(118), 3557-3561

Author Affiliation:
[1]MD Second Year Pathology, Department of Pathology, Sree Balaji Medical College and Hospital, Chrompet, Chennai, Tamilnadu, India
[2]Senior Resident, Department of Pathology, Sree Balaji Medical College and Hospital, Chrompet, Chennai, Tamilnadu, India
[3]Associate Professor, Department of Pathology, Sree Balaji Medical College and Hospital, Chrompet, Chennai, Tamilnadu, India

✉**Corresponding author**
MD Second Year Pathology, Department of Pathology, Sree Balaji Medical College and Hospital, Chrompet,
Chennai, Tamilnadu, India
Email: drammoorthyvc@gmail.com

Peer-Review History
Received: 08 November 2021
Reviewed & Revised: 09/November/2021 to 24/December/2021
Accepted: 26 December 2021
Published: December 2021

Peer-review Method
External peer-review was done through double-blind method.

ABSTRACT

Many rheumatic conditions, including Systemic sclerosis, increase the risk of cancer. Solid tumours are most often found in the lungs, oesophagus, or breast. A higher risk of haematological cancers also associated with some DMARD therapeutic drug for systemic sclerosis. Myelodysplastic syndrome develops as a result of DMARD therapy used to treat systemic sclerosis, especially the drug azathioprine and cyclophosphamide, which has been linked to increase risk of developing myelodysplastic syndrome as compared to mycophenolate mofetil and methotrexate, according to reports. Another research found that a low dose of methotrexate can cause myelodysplastic syndrome in people with rheumatoid arthritis. There has been a rare reported case of myelodysplastic syndrome (MDS) secondary to Systemic sclerosis in some literature. Our goal is to raise concern about the growing prevalence of Myelodysplastic Syndrome in patients with Systemic Sclerosis that have been treated with azathioprine, cyclophosphamide and methotrexate, as was the scenario in our case.

Keywords: Sclerosis; Azathioprine; Myelodysplastic; Methotrexate; Haemopoietic tissue.

1. INTRODUCTION

As Rheumatic disease like Systemic sclerosis can cause mostly Lymphoproliferative disorders (like B-cell lymphomas) and also are associated with rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematous. In contrast to solid tumours, the probability of having myelodysplastic syndrome followed by acute myeloid leukaemia is lower in people with systemic sclerosis (Abraham, 2009). There was refractory anaemia with excess blasts and a pre-leukemic conditions as well as clonal abnormality of hematopoieticstem cells were seen in the forms of Myelodysplastic syndrome secondary to systemic sclerosis (Leone, 2007). Mutant agents or

irradiation are unlikely to be the cause of Myelodysplastic syndrome in systemic sclerosis (Heidi, 2007). However, long-term immune dysfunction, which is found in these collagen diseases, also plays vital role in causation of this myelodysplastic syndrome.

In our situation, the main cause of myelodysplastic syndrome may be following the onset of an autoimmune illness such as systemic sclerosis was the initiation of DMARD treatment with injection cyclophosphamide and azathioprine (Okamoto, 2004).

2. CASE PRESENTATION

A 39 years old female known case ofscleroderma (Systemic sclerosis) for past 9 years associated Interstitial lung disease since 5 years on was on immunosuppressant DMARD therapy with Mycophenolatemofetil, Prednisolone, Azathioprine, Methotrexate and cyclophosphamide) admitted with complaints of severe right sided headache for past 5 days, which gets relieved on taking analgesics. Complaints of palpitation and NYHA grade III breathlessness on minimal exertion for past 3 months for which she was on theophylline and calcium channel blockers. She also has complaints of burning micturition, generalized tiredness, giddiness associated with postural change and excessive hair loss present for past 5 months. Inmenstrual history, patient had complaints of irregular menses associated with whitish discharge for above 10 years.

On examination patient is Conscious, oriented, Pallor present, clubbing present, local examination revealed swelling and tenderness present overthe distal inter-phalangeal joint, proximal inter-phalangeal joint and metatarsophalangeal joints involving both hands. Range of movement's reduced. Nodules present over the left elbow, lateral border of both foot and in left index finger. On systemic examination: Tachycardia present, Respiratory system: Bilateral air entry reduced with bilateral crepitation's present, per abdomen: Soft, diffuse lower abdominal tenderness present.

Blood investigation done revealed elevated ESR-100 millimetres per hour; Haemoglobin of 4.4 gm. /dl Red blood cell indices like MCV-141 FL and MCH-40.3 pg.are increased along with decreased RBC count of 1.08million/mm3.Peripheral smear study revealed RBC with Dual population of microcytes (Figure 1). Tear drop cells, nucleated RBC's and foci of autoagglutinations, rouleaux formation are also noted (Figure 2); WBC showed normal count with shift to left and few apoptotic neutrophils are also seen (Figure 3). Platelets was adequate. No Haemoparasites seen. Hence, Picture is suggestive of dimorphic anaemia (Predominantly macrocytosis) which favours the diagnosis of dyserythropoietic picture of drug induced Myelodysplastic syndrome.

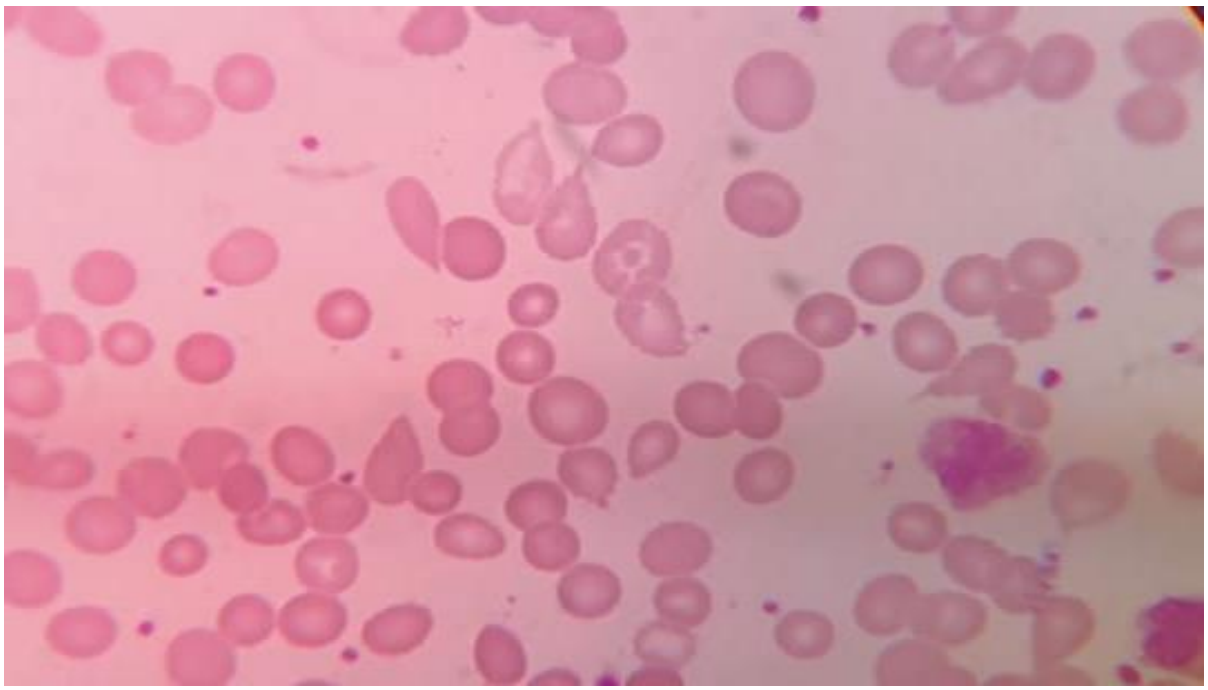

Figure 1 dual population of microcytic rbcs admixed with predominant macrocytic rbcs with moderate anisopoikilocytosis showing tear drop cells.

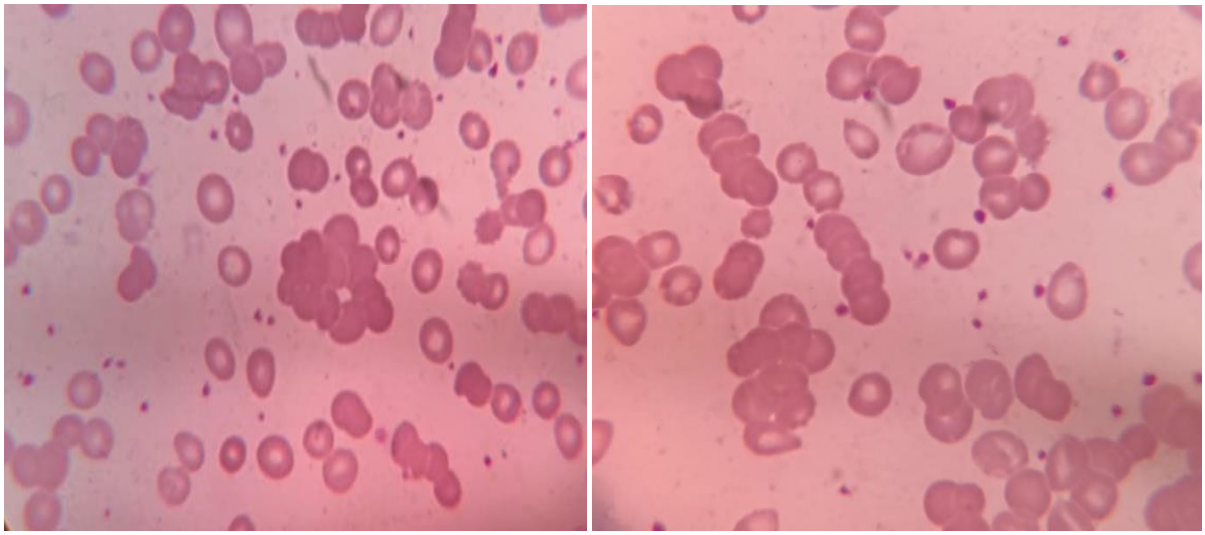

Figure 2 autoagglutination and rouleaux formation seen together.

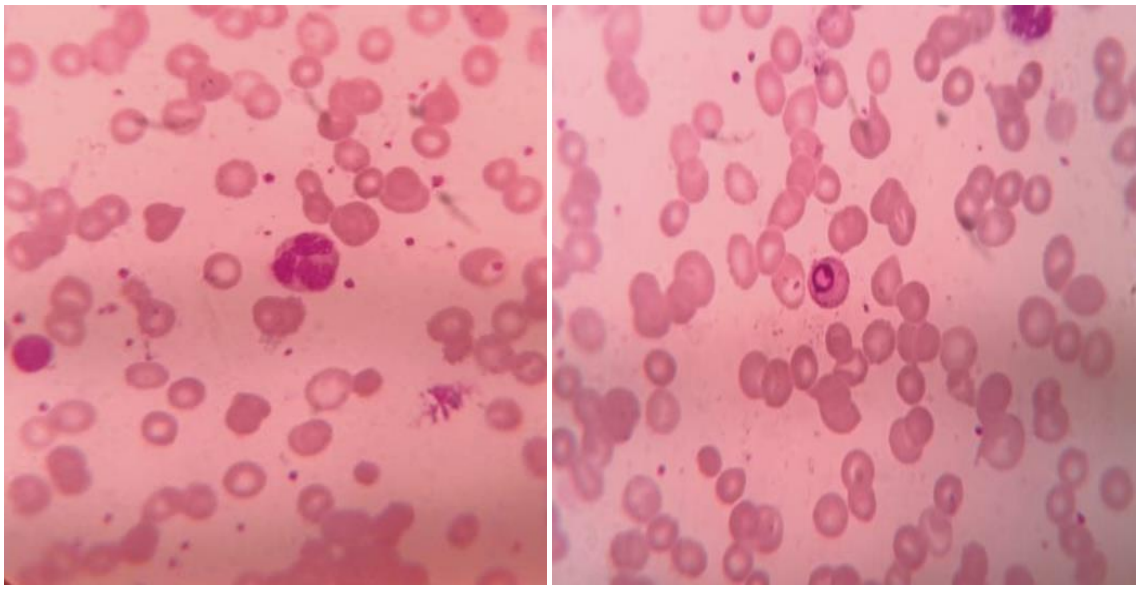

Figure 3 apoptotic neutrophils seen.

HRCT chest revealed honey combing pattern with marked pulmonary fibrosis and ground glass opacities involving the basal pulmonary segments, compromising especially the peripheral and posterior parenchyma's and Chest X ray revealed pulmonary reticulation diffusely involving both lung fields -both suggesting to features of interstitial lung disease.

3. DISCUSSION

Several studies in patients with Systemic sclerosis have shown an improved risk of cancer, especially lung cancer, as well as other diseases such as non-melanoma skin cancer, non-lymphoma, Hodgkin's oesophageal cancer, and liver cancer (Takashima, 1994). Some studies suggest that in the first year of diagnosis of Systemic sclerosis there is risk of development of cancer is higher while others suggest that occurrence of cancer is higher.

Myelodysplastic syndrome is a haematological condition marked by dysplastic and inadequate haematopoiesis that may progress to acute leukaemia (Hamamoto, 1996). Haematological cancers such as non-Hodgkin lymphoma, leukaemia, multiple myeloma, and myeloproliferative neoplasms have been identified in Systemic sclerosis patients in several cohorts, prospective, retrospective, and case control trials. Olesen (2010) found a 2.5-fold elevated prevalence of haematological cancers in a national population-based cohort survey. Hematologic malignancies can cause Para-neoplastic scleroderma (Chatterjee, 2005). Myelodysplastic syndrome caused by rheumatoid arthritis, systemic lupus erythematous, Sjogren's disease, or Sjogren's syndrome

is highly unusual. A few case studies and episodes, on the other hand, identified patients with Systemic sclerosis and Myelodysplastic syndrome.

Both Systemic sclerosis and Myelodysplastic syndrome have a multifactorial pathogenic pathway including genetic and environmental causes. Except for anti-RNA polymerase III for Para-neoplastic scleroderma, there is no direct correlation between anti-centromere and anti-Scale 70 antibodies and cancer risk. Immunosuppression, chronic B-cell activation, anti-rheumatic medications like cyclophosphamide, azathioprine, methotrexate, and chromosomal defects are also suspected risk factors for hematologic malignancies in Systemic sclerosis patients which are also evident in our case (Szekanecz, 2012). It's also suspected that DNA disruption from oxidative stress, as well as a weak genome and chromosomal defects, are seen in Systemic sclerosis, which may have paved the way for the development of Myelodysplastic syndrome in conjunction with cytotoxic DMARD medications such as cyclophosphamide, azathioprine, and methotrexate (Pan, 1975).

In our case, Patient with Systemic sclerosis show haematological lab values revealing anaemia with Hb-4.4 gm./dl increased MCV, increased MCH and reduced RBC count. Peripheral smear study revealed RBCs with dual population of microcytes (Onishi, 2013). Tear drop cells, nucleated RBC's and foci of auto-agglutinations are also noted. WBC's which are normal in number with shift to left and picture is suggestive of dimorphic anaemia (Predominantly macrocytosis) -dyserythropoietic picture which is in favour of Myelodysplastic syndrome (Olesen, 2010).

The stoppage/discontinuation of cytotoxic DMARD medications such as cyclophosphamide, azathioprine, and methotrexate is advisable and a change of regimen in DMARD therapy with the efficacy of steroids for Systemic sclerosis-associated Myelodysplastic syndrome (Shah, 2011). So, DMARD therapy regimen with rituximab and azacytidine seem to be promising. For correction of haematological parameters like pancytopenia, 20 mg/body weight methenolone orally, which led to haematological improvement after 6 month (Avouac, 2010).

4. CONCLUSION

Both Systemic sclerosis and Myelodysplastic syndrome have a multifactorial pathogenic pathway including genetic and environmental causes. It's also suspected that DNA disruption from oxidative stress, as well as a weak genome and chromosomal defects, are seen in Systemic sclerosis, which may have paved the way for the development of Myelodysplastic syndrome in conjunction with cytotoxic DMARD medications such as cyclophosphamide, azathioprine, and methotrexate. In our case, Patient with Systemic sclerosis show haematological lab values revealing anaemia with Hb-4.4 gm. /dl; increased MCV, increased MCH and reduced RBC count. Peripheral smear study revealed RBCs with dual population of microcytes. Tear drop cells, nucleated RBC's and foci of auto-agglutinations are also noted. WBC's which are normal in number with shift to left and picture is suggestive of dimorphic anaemia (Predominantly macrocytosis) -dyserythropoietic picture which is in favour of Myelodysplastic syndrome. DMARD therapy regimen with rituximab and azacytidine seem to be promising. For correction of haematological parameters like pancytopenia, 20 mg/body weight methenolone orally, which led to haematological improvement after 6 months.

Acknowledgement

We express our heartfelt gratitude to Dean Sree Balaji Medical College and Hospital (SBMCH), Chrompet, Chennai, Tamilnadu, India, for providing us with the chance to conduct this research. We would like to thank HOD, Department of Pathology, Sree Balaji Medical College and Hospital Chennai, for her unwavering support and encouragement. We'd also want to express our gratitude to the Medical Superintendent of Sree Balaji Medical College and Hospital for enabling us to conduct the experiment with hospital equipment, facilities, and patients. We owe a debt of gratitude to the subject for putting out the effort that allowed the experiment to take place.

Informed consent

Written & Oral informed consent was obtained.

Funding

This study has not received any external funding.

Conflict of Interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are presented in the paper.

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